Spring 5-1-2015

Methodology Development in Green Chemistry: Oxoammonium Salt Oxidations and Fluoroform Incorporation

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University of Connecticut, 2015

A Thesis

Submitted in Partial Fulfillment of the

Requirements for the Honors Program at the

University of Connecticut

2015

Abstract

Central to the advancement of small molecule synthesis is the ability to develop methodologies that reimagine well known chemistry in a new, environmentally friendly manner. In this thesis two central themes emerge: oxoammonium salt oxidations and trifluoromethyl incorporation using fluoroform gas. Several projects have been developed surrounding oxoammonium salt chemistry, which are featured by their mild conditions, ease of use, and the metal-free, recyclable nature of the oxidant. Trifluoromethylation using fluoroform gas finds its utility in the use of a potent greenhouse gas waste product as a benchtop reagent.

Acknowledgements

This work would not have been possible without the immeasurable help of several individuals and organizations. Many thanks are owed to Dr. Nicholas Leadbeater for his years of guidance and for making this research possible. I am very grateful to have been able to join his group so early in my career, and to be able to participate in so many diverse research opportunities. I would like to thank Christopher Kelly, Michael Mercadante, John Ovian, and the rest of the Leadbeater lab for their contributions to and mentorship on these projects. Thank you to Prof. Leon Tilley at Stonehill College for taking me as a summer student and for his work on collaborative projects with our group. I would also like to thank Prof. William Bailey and Prof. Mark Peczuh for their participation on my University Scholar Committee. Thank you to the University of Connecticut Honors Program, the University Scholar Program, and the Office of Undergraduate Research for supporting this research. Finally, I would like to thank my friends and family for their continued support throughout my undergraduate career.

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List of Abbreviations

AcO	Acetate
Ar	Aryl
atm	Atmosphere
Bn	Benzyl
$CDCl_3$	Deuterated chloroform
^{O}C	Degrees Celsius
CDI	1,1'-Carbonyldiimidazole
$-CF_3$	Trifluoromethyl
CHF_3	Fluoroform
DCM	Dichloromethane
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Eq.	Molar equivalent
EWG	Electron-withdrawing group
g	Gram
GWP	Global warming potential
HFIP	Hexafluoroisopropanol
HMDS	Hexamethyldisilane
HOAc/NaOAc	Acetic acid/sodium acetate
KHMDS	Potassium bis(trimethylsilyl)amide
KO^{t}Bu	Potassium *tert*-butoxide
MeCN	Acetonitrile
n-Bu	*n*-Butyl
NMR	Nuclear magnetic resonance
Ph	Phenyl
r.t.	Room temperature
TBAF	Tetrabutylammonium fluoride
^{t}Bu	*tert*-Butyl
TFE	2,2,2-Trifluoroethanol
TFMK	Trifluoromethyl ketone
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS, Me_3Si	Trimethylsilyl
TMS-CF_3	Trimethyl(trifluoromethyl)silane

List of Publications

Oxidative Esterification of Aldehydes via an Oxoammonium Salt Kelly, C. B.; Mercadante, M. A.; **Wiles, R. J.**; Leadbeater, N. E. *Org. Lett.* **2013**, *15*, 2222.

Oxidative Cleavage of Allyl Ethers by an Oxoammonium Salt Kelly, C. B.; Ovian, J. M.; Cywar, R. M.; Gossland, T. R.; **Wiles, R. J.**; Leadbeater, N. E. *Org. Biomol. Chem.* **2015**, *13*, 4255.

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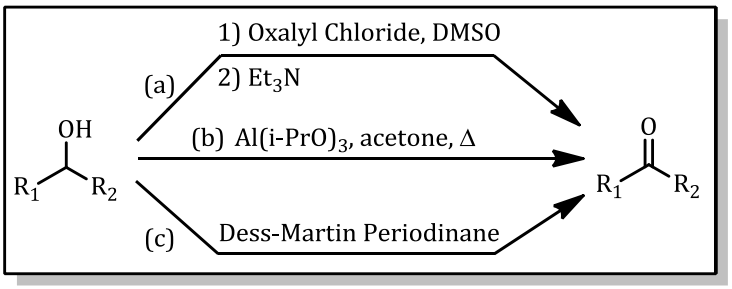
Chapter 1: Background on Oxoammonium Salts

One of the most well-researched and versatile class of synthetic transformations is oxidation chemistry. Oxidation can occur through a multitude of pathways and exists under many definitions. Whether it be the classic "loss of electrons is oxidation, gain of electrons is reduction" or the organic chemist's perspective of "addition of hydrogen is reduction, addition of oxygen (or electronegative atom) is oxidation," oxidation chemistry can be both incredibly simple or intricate and complex. One of the most common oxidative transformations is the conversion of an alcohol to a carbonyl species. Some common named reactions of this type include the Swern[1], Oppenauer[2], and the Dess-Martin periodinane[3] oxidations (Scheme 1), among many more. Each of these reactions comes with its own drawbacks, whether it be in ease of use, reaction efficiency, or cost, respectively. In the interest of circumventing these drawbacks, it would be advantageous to develop an alternative oxidation method.



Scheme 1 Examples of common named oxidation reactions (a) Swern (b) Oppenauer (c) Dess-Martin

Oxoammonium salts have recently surfaced as highly promising reagents for developing new oxidation methods. They have several advantages over other reagents. The salts are free of heavy metals and thus more environmentally friendly than other common oxidants, and are also recyclable and so can be recovered in good yield after a reaction is complete. Additionally, oxoammonium salts have proven on many occasions to be user-friendly and functional under mild reaction conditions. One of the first oxoammonium species discovered was TEMPO, tetramethylpiperidyl oxyl, (Figure 1(a))[4], which is often employed as a catalyst for the oxidation of primary alcohols to aldehydes. More recently, one particular oxoammonium salt has caught the attention of organic chemists due to its

[1] *(a)* Tidwell, T. T.; *Org. React.*, **1990**, *39*, 297 *(b)* Mancuso, A. J.; Huang, S.-L.; Swern, D.; *J. Org. Chem.*, **1978**, *43*, 2480

[2] *(a)* Oppenauer, R. V.; *Recl. Trav. Clim. Pays-Bas*, **1937**, *56*, 137 *(b)* Graves, C. R.; Campbell, E. J.; Nguyen, S. T.; *Tetrahedron*, **2005**, *16*, 3460 *(c)* Mandell, L.; *J. Am. Chem. Soc.*, **1956**, *78*, 3199

[3] *(a)* Dess, D. B.; Martin, J. C.; *J. Org. Chem.*, **1983**, *48*, 4155 *(b)* Tohma, H.; Kita, Y.; *Adv. Synth. Catal.*, **2004**, *346*, 111

[4] Lebedev, O. L.; Kazarnovskii, S. N.; *Zhur. Obshch. Khim.*, **1960**, *50*, 1631

potential applications to a wide variety of transformations. The salt, 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, **1**, is more commonly known as Bobbitt's Salt (Figure 1 (b))[5,6]. This salt is a stoichiometric oxidant that can easily be prepared in-house for about $0.50 per gram, or can be purchased at about $7 per gram from conventional sources. Additionally, an intermediate isolated in the preparation of this salt (Figure 1 (c)) has a utility of its own, as it can be used as a catalyst in oxidations that employ a stoichiometric terminal oxidant.

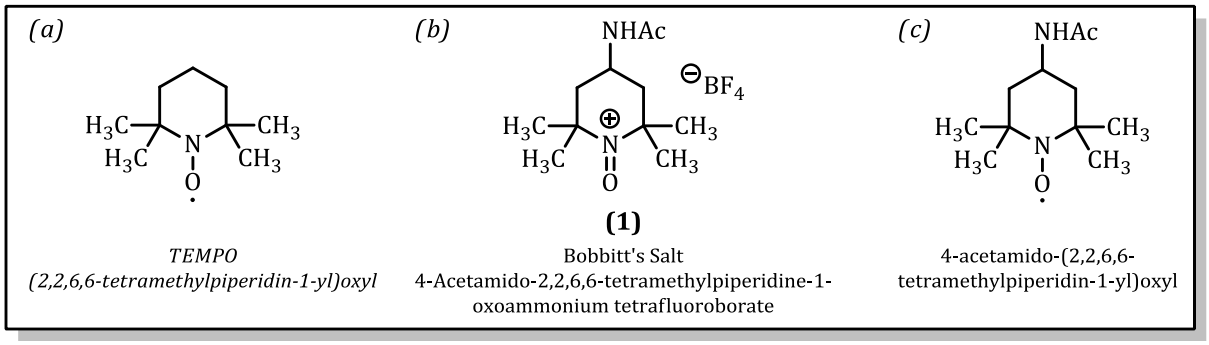
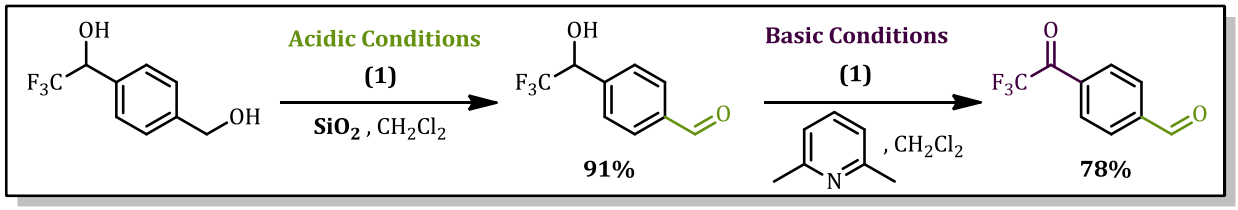


Figure 1 TEMPO and its derivative "Bobbitt's Salt"

Much of the early work using **1** involved the oxidation of alcohols to aldehydes and ketones.[7] The original conditions feature a slightly acidic medium due to the addition of silica gel (Scheme 2). These conditions allow for the selective oxidation of a range of alcohol substrates. A more recent procedure outlined the use of 2,6-lutidine to effect basic conditions, which allows for the oxidation of harder-to-oxidize substrates, such as α-CF_3 alcohols.[8]

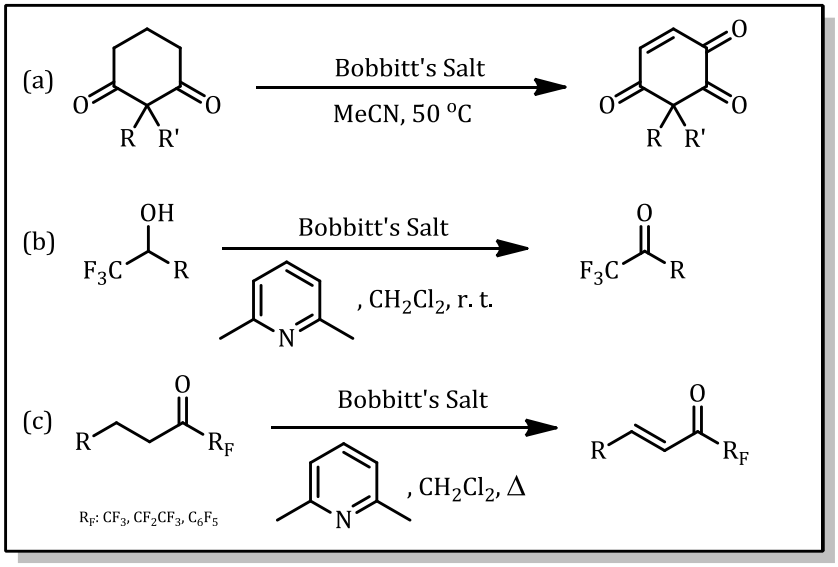


Scheme 2 Bobbitt's Salt oxidations under acidic and basic conditions

Looking to expand the profile of reactions available using the salt, the Leadbeater group along with several collaborators worked to develop numerous new oxidation methods. In a joint project with the Fenteany group, a method was developed to access ene-triketones via the oxidation of diketones (Scheme 3 (a)).[9] Another particularly interesting

[5] Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E.; *Nat. Protoc.* **2013**, *8*, 666
[6] Leadbeater, N. E.; Bobbitt, J. M.; *Aldrichim. Acta*, **2014**, *47*, No. 3
[7] Bobbitt, J. M.; *J. Org. Chem.*, **1996**, *63*, 9367
[8] Kelly, C. B.; Mercadante, M. A.; Hamlin, T. A.; Fletcher, M. H.; Leadbeater, N. E.; *J. Org. Chem.,* **2012**, *77*, 8131
[9] Eddy, N. A.; Kelly, C. B.; Mercadante, M. A.; Leadbeater, N. E.; Fenteany, G.; *Org. Lett.*, **2012**, *14*, 498

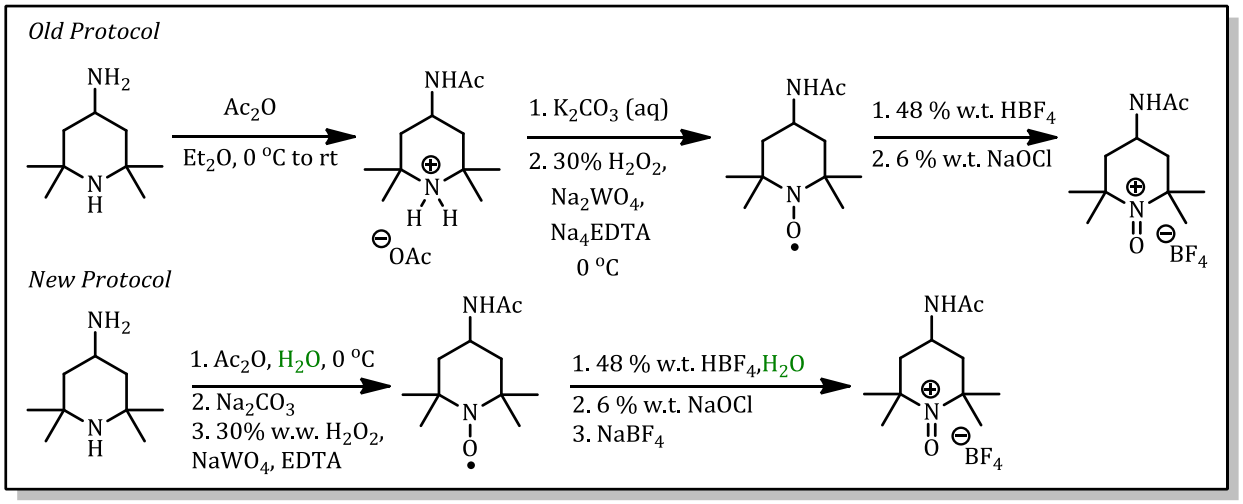
project involved the oxidation of CF_3 alcohols (Scheme 3 (b)). Historically, α-fluorinated alcohols have proven difficult to oxidize due to the electron deficient nature of the CF_3 group. Using the original conditions developed by Bobbitt where silica gel is used to maintain an acidic environment, the oxidation does not occur; however, performing the reaction under basic conditions, either by addition of 2,6-lutidine for activated systems or DBU for unactivated systems, this challenging transformation could be accomplished. While exploring the scope of this reaction, an interesting over-oxidized dehydrogenation side product was observed. With the aim of exploiting this unusual result, the group went on to publish a method for the efficient oxidative dehydrogenation of perfluoroalkyl ketones (Scheme 3 (c)).[10]



Scheme 3 Previous work with Bobbitt's Salt by the Leadbeater group

As previously mentioned, it is possible to purchase the oxoammonium salt **1** from conventional sources; however, it is far more cost effective to prepare the salt in-house. As **1** is used in stoichiometric amounts, it became clear that an optimal route to its preparation would be highly advantageous. Luckily, the salt has been proven to be incredible shelf stable for extended time periods, and thus can be kept on-hand in large quantities. The original protocol for preparation of **1** was three steps and performed in both ethereal and aqueous conditions (Scheme 4). The Leadbeater group revised this protocol to require only two isolations and to take place completely in aqueous conditions, greatly enhancing its profile as an environmentally friendly oxidant.

[10] Hamlin, T. A.; Kelly, C. B.; Leadbeater, N. E.; *Eur. J. Org. Chem.*, **2013,** 3658



Scheme 4 Developments in the Oxoammonium Salt Preparation Protocol

Further studies of **1** were aimed at expanding the utility of the salt for non-traditional oxidation reactions. It is the ongoing goal of the Leadbeater group to continue demonstrating how versatile and robust Bobbitt's salt oxidations can be, and thus have developed several new methodologies in the last few years. The projects of which I have taken part are described in the following sections.

Chapter 2: Methodology Developments with Oxoammonium Salts

2.1 Oxidative Esterification

Introduction

Of the many potential carbonyl species that may be targets for oxoammonium salt oxidation, we first turned our attention to esters. Esters have a number of properties that make them useful compounds in their own right as well as versatile building blocks for more complex organic molecules. While generally being shelf stable molecules, esters may also be easily converted into other functional groups or as starting materials for polymer construction. The traditional method of ester preparation is through activation of carboxylic acids followed by reaction with an alcohol coupling partner, known as the Fischer esterification.[11] Some classic esterification reactions include activation with reagents such as $SOCl_2$, DCI, DEAD/PPh_3, and DCC (Figure 2).[12] Each of these reactions comes with its own set of drawbacks, whether it be functional group intolerance or high levels of toxicity or hazard to the user.

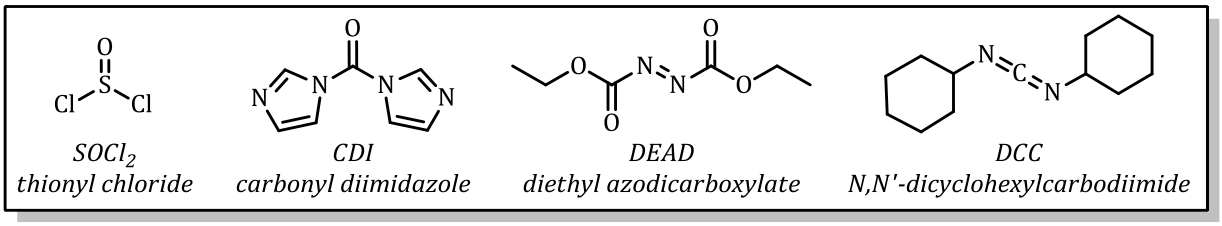


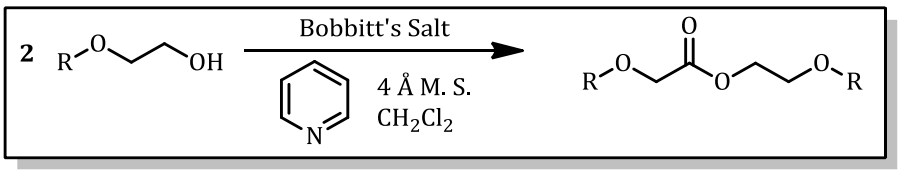
Figure 2 Common activation methods for esterification reactions

As an alternative to carboxylic acid activation, a new approach is emerging that utilizes a tandem oxidation-esterification process. One major benefit to this class of reactions is a greater level of flexibility in the aldehyde starting material. In the last several years, a number of approaches have been developed that follow this process. Some of the most versatile and well-known methods include activation by *N*-heterocyclic carbenes,[13] transition metal-mediated processes,[14] and those that use a stoichiometric oxidant in the

[11] Fischer, E.; Speier, A.; *Chemische Berichte,* **1895**, *28*, 3252
[12] *(a)* Otera, J.; *Esterification: Methods, Reaction and Application,* 2nd Ed.; Wiley-VCH: Weinheim, **2010** *(b)* Riemenschneider, W.; Bold, H. M.; *Esters, Organic. Ullmann's Encyclopedia of Industrial Chemistry*: Wiley-VCH: Weinheim, **2005** *(c)* Rosato, D. V.; Rosato, D. V.; Rosato, M. V.; *Plastic Product Material and Process Selection Handbook*: Elesevier Inc.: New York, **2004** *(d)* Staab, H. A.; Mannschreck, A.; *Chem. Ber.*, **1962**, *95*, 1284 *(e)* Mitsunobu, O.; *Synthesis*, **1981**, *1 (f)* Dembinski, R.; *J. Org. Chem.*, **2004**, 2763 *(g)* Neises, b.; Steglich, W.; *Angew. Chem. Int. Ed.*, **1978**, *17*, 522
[13] Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 4331.
[14] Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.

presence of an alcohol coupling partner.[15] This last class of oxidative esterifications inspired our new approach using **1** as the oxidant.

Prior to our research, there was little work done on esterification using an oxoammonium salt. The most notable example was a method developed by Bobbitt that reports that alcohols can be converted into their dimeric esters (Scheme 5).[16] Unfortunately, the reaction scope is limited to alcohols that contain β–oxygen substituents. Esterification in substrates that did not contain the β–oxygen moiety was seen only in limited yields.



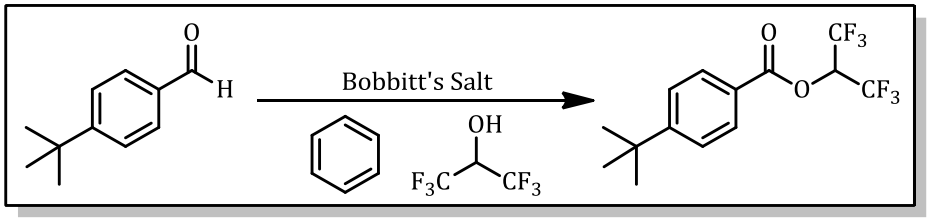
Scheme 5 Bobbitt's protocol for dimeric ester synthesis

Hoping to develop a more versatile oxoammonium salt-mediated esterification, we turned to the possibility of coupling an aldehyde with an alcohol partner. Prior to beginning optimization, the obvious problem of alcohol oxidation needed to be addressed. As mentioned, alcohols have a high propensity for oxidation to their corresponding aldehydes or ketones. In order to pursue this transformation, an alcohol that would not preferentially oxidize under the reaction conditions needed to be selected. Based on the previous work in the Leadbeater lab oxidizing α–CF_3 alcohols, we knew fluorinated alcohols to be relatively unoxidizable when in the presence of pyridyl bases. For this reason, we chose hexafluoroisopropanol (HFIP) as our alcohol coupling partner. Under the reaction conditions HFIP does not oxidize in significant quantities. Additionally, fluorinated esters are valuable products as they can be easily converted to other functional groups due to the ease of perfluoro alcohol removal. With the knowledge of the potential impact of this method in hand, we began optimization and substrate scope studies.

Results and Discussion

Optimization studies were performed on *p-tert*-butylbenzaldehyde as this represents a midpoint between electron rich and poor systems, as well as having a high molecular weight to allow for easy isolation of the ester product (Scheme 6).

[15] Tschaen, B. A.; Schmink, J. R.; Molander , G. A. *Org. Lett.*, **2013**, *15* , 500
[16] Merbouh, N.; Bobbitt, J. M.; Bruckner, C.; *J. Org. Chem.*, **2004**, *69*, 5116



Scheme 6 Optimization model

Our preliminary study used 2.2 equiv. of pyridine, 2.5 equiv. of Bobbitt's salt, and 1.5 equiv. HFIP in 0.5 M DCM, giving 70% yield by GC/MS in 12 hours (Table 1, Entry 1). This result gave us a good starting point for optimization, but both the yield and reaction time needed improvement. Next we increased the loading of HFIP to 3 equiv. and utilized the pyridine as both the base and the solvent (12.75 equiv.), and were able to detect complete conversion in just 1 hour (Table 1, Entry 2). Isolation of the resulting HFIP ester was achieved in 96% yield. We then attempted to reduce the equivalents of HFIP but this necessitated a longer reaction time, so the original loading was used (Table 1, Entry 3). Two other pyridyl bases were examined, 4-picoline and 2,6-lutidine, but pyridine gave optimal results (Table 1, Entries 4 and 5).

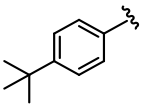
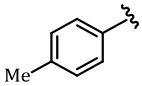
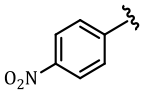
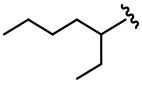
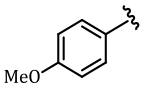
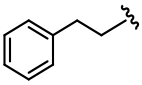
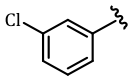
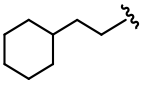
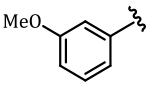
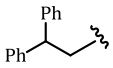
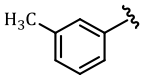
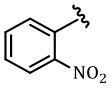
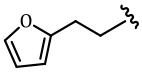
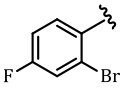
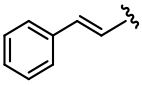
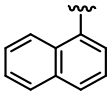
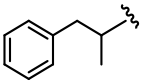
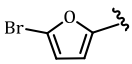
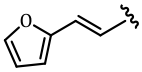
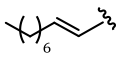
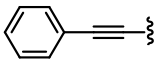
Table 1 Optimization studies for oxidative esterification

Entry	Base	Salt	HFIP	Solvent	Time	Conversion
1	2.2 eq. pyridine	2.5 eq.	1.5 eq.	0.5 M DCM	12 hr	70%
2	12.75 eq. pyridine	2.5 eq.	3 eq.	Pyridine	1 hr	100%
3	12.75 eq. pyridine	2.5 eq.	2 eq.	Pyridine	6 hr	100%
4	12.75 eq. picoline	2.5 eq.	3 eq.	4-picoline	1 hr	100%
5	12.75 eq. lutidine	2.5 eq.	3 eq.	2,6-lutidine	1 hr	100%

We followed this optimization study with an examination of substrate scope. We screened a number of different derivatives of benzaldehyde, including both electron poor and electron rich aryl rings (Table 2.1). Both electron poor (Entries 3, 5, 8, 9) and electron rich (Entries 1-2, 4, 6-7) examples underwent oxidation and gave high yields of their corresponding HFIP esters. The highest rate of conversion was seen in substrates with electron poor aryl systems. Some examples (Entries 3, 4, 9, 16, 18, 23, and 24) did not go to complete conversion under the specified conditions, and required additional Bobbitt's salt and HFIP. With these additions, complete conversion was seen in those substrates. We then probed more complex R-groups such as polycyclic and heterocyclic rings. We were

successfully able to oxidize furyl and pyridyl substituted aldehydes in excellent yields (Entries 11, 12, and 13), as well as 1-napthaldehyde in high yield (Entry 10).

Table 2 Scope of oxidative esterification of various aldehydes with HFIP

Entry	R	Yield (%)[b]	Entry	R	Yield (%)[b]
1		96[c]	**14**		79
2		94[c]	**15**		75[c]
3		89[b]	**16**		86[b,c]
4		95[b]	**17**		87[c]
5		94	**18**		70[b,c]
6		79	**19**		87
7		90	**20**		-
8		94	**21**		68
9		96[b]	**22**		78[c]
10		86	**23**		91[b,c]
11		91[c]	**24**		91[b]
12		88[c]	**25**		-
13		95[c]	**26**		-

We then wished to extend the scope of this reaction to aliphatic aldehydes. We found that systems without α-substitution (Entry 14) oxidized well under our conditions. Those systems with α-substitution (Entries 16 and 23) tended to react slower, and ultimately required additional Bobbitt's salt and HFIP to proceed to completion. The reduction in rate was likely due to steric hindrance of the α–substituents. Interestingly, this phenomenon was not observed in the cyclohexyl system (Entry 15) which could be hypothesized to be caused

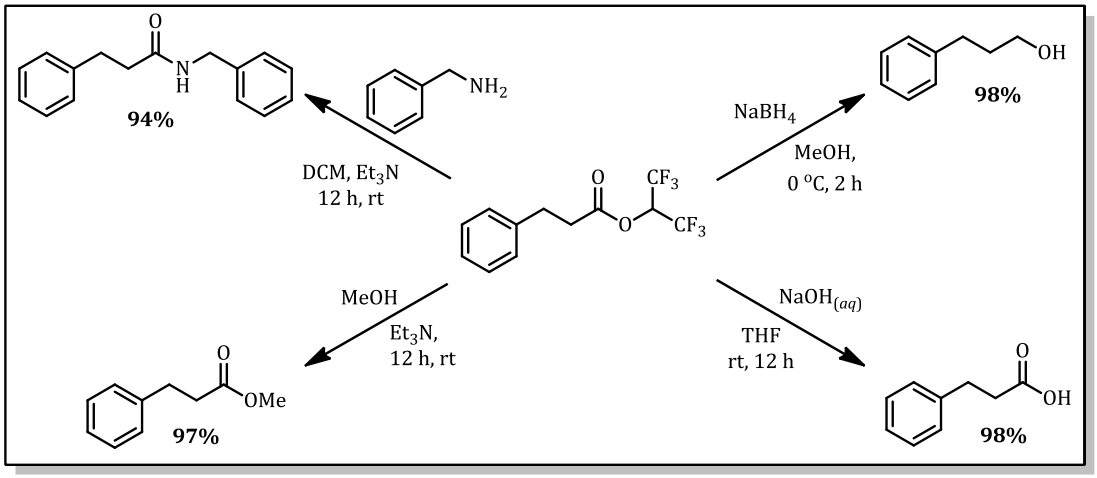
by the restricted rotation of the ring structure. When the substrate was substituted at the β position, the reaction proceeded as normal. An anomaly in this series of substrates was the α-diphenyl system (Entry 20) which gave neither product nor left unreacted starting material. This result may have been due to the heightened acidity of the α–proton, causing the formation of either an α–alkylation product between the enol and Bobbitt's salt or a polymer-forming series of aldol-like reactions.

The third class of compounds we explored included α,β-unsaturated and propargylic systems. Some olefinic species, such as cinnamyl and furylacryl (Entries 22 and 24) were successfully oxidized under the proposed conditions, while α–methyl cinnamaldehyde did not go to complete conversion. Similarly, a non-conjugated α,β-unsaturated aldehyde and its corresponding alkynyl aldehyde gave no product, and only resulted in polymeric material.

As a final step in the substrate scope experimentation, we explored the possibility of using trifluoroethanol (TFE) as the non-oxidizable alcohol. Taking three representative aldehydes (Entries 2, 3, and 4), we tested the standard reaction conditions as well as the higher salt and alcohol loading conditions. Unfortunately, we were never able to isolate the products in more than 30% yield.

Upon completion of the substrate scope, we transitioned to demonstrating the applicability of the HFIP ester products. Four application reactions were selected and tested using the product of Entry 17 (Scheme 7). First, we tested the propensity of the ester for reduction and found that it was readily reduced with $NaBH_4$. This was quite a remarkable finding, considering esters are generally not reactive enough to be reduced by $NaBH_4$ and usually require more harsh reducing agents such as $LiAlH_4$.[17] The second application reaction was a transesterification to the corresponding methyl ester, which was readily accomplished with trimethylamine in methanol at room temperature. We then showed that the HFIP ester was reactive under transamination conditions. Finally, we showed that the ester could be hydrolyzed to its corresponding carboxylic acid. One question surrounding these applications is why go through the ester intermediate to transform from the aldehyde to any of the application products. The logic behind this method is that the HFIP esters are both reactive and highly shelf stable, so it is easy to see the benefits of storing compounds as the esters when either the starting material or product degrades over time.

[17] Nystrom, R. F.; Brown, W. G.; *J. Am. Chem. Soc.*, **1947**, *69*, 1997



Scheme 7 Applications Reactions of HFIP ester synthesis

Conclusions

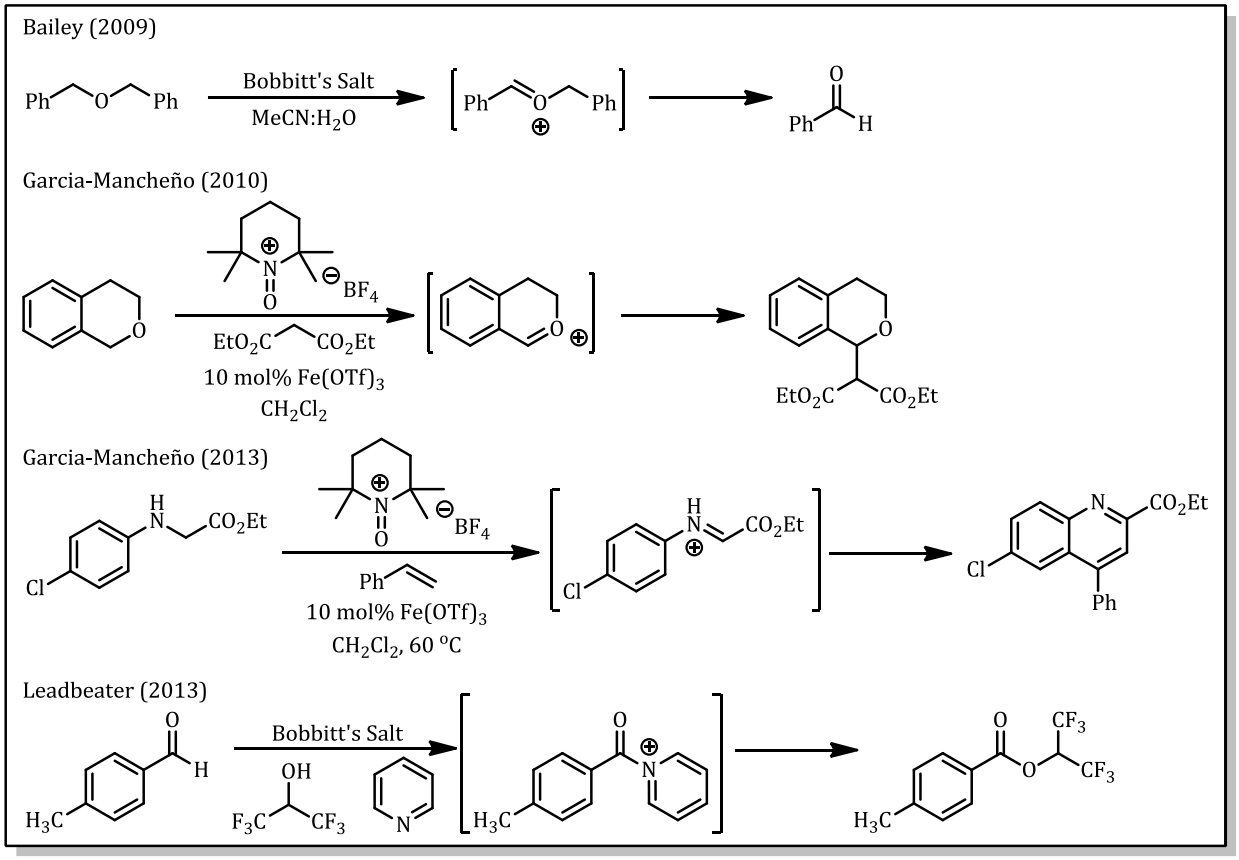
In summary, we developed a versatile and synthetically useful oxoammonium salt mediated oxidative esterification reaction. The reaction is conducted under mild conditions and in a short period of time. A wide range of substrates have been confirmed to be compatible with the reaction setup and isolated in high yields. The resulting HFIP esters are shelf-stable and have been shown to be reactive towards a number of further functionalization reactions.

2.2 C-H Bond Functionalization

Introduction

Upon completion of the oxidative esterification, we transitioned to a slightly different class of reactions: C-H bond functionalization. This area of research is of broad interest to the synthetic chemist because the C-H bond is relatively inert compared to more activated groups such as halides, pseudohalides, and other leaving groups. Many modern C-H functionalization reactions are mediated by transition metal catalysis, which is often quite costly.[18] Our goal was to transition our knowledge of oxoammonium salt oxidations to the field of C-H functionalization in order to provide an inexpensive, easy-to-perform, and environmentally friendly alternative to transition metal catalysis.

[18] Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson; *Acc. Chem. Res.,* **1995**, *28*, 154



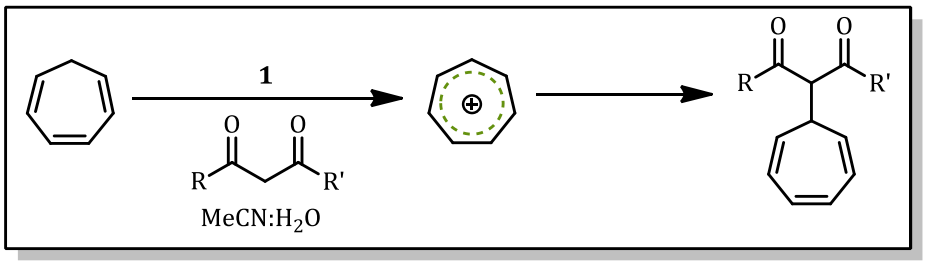
Scheme 8 Previous Examples of Oxidative Functionalization with Oxoammonium Salts

Previous studies in the area of oxoammonium salt mediated functionalization have been performed by Bailey, Garcia-Mancheño, and the Leadbeater group (Scheme 8).[19] The Bailey method is of particular interest to us, as he successfully cleaved benzyl ethers using Bobbitt's salt as the oxidant. This type of reaction has important implications for the protection and deprotection of alcohols. In common with both the Bailey method and the García-Mancheño method is that a fairly acidic benzylic C-H bond is functionalized. Our group had the hopes of taking this reaction one step further by exploring the possibility of functionalizing a less reactive C-H bond, that which is part of an allyl ether system. The potential utility of this reaction was two-fold: to develop a route to prepare α,β-unsaturated aldehydes as well as develop an alternative protection and deprotection strategy for allyl alcohols.

As a second object of our C-H bond functionalization goals, we sought to develop a method for the activation and functionalization of cycloheptatriene using Bobbitt's salt (Scheme 9). We became interested in this substrate because it presented an interesting

[19] *(a)* Richter, H.; Rohlmann, R.; García Mancheño, O.; *Chem. Eur. J.*, **2011**, *17*, 11622 *(b)* Richter, H.; García Mancheño, O.; *Org. Lett.*, **2011**, *13*, 6066 *(c)* Richter, H.; Fröhlich, R.; Daniliue, C.-G.; García Mancheño, O.; *Angew. Chem. Int. Ed.*, **2012**, *51*, 8656 *(d)* Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F.; *J. Org. Chem.*, **2009**, *74*, 9524 *(e)* Kelly, C. B.; Mercadante, M. A.; Wiles, R. J.; *Org. Lett.*, **2013**, *15*, 222

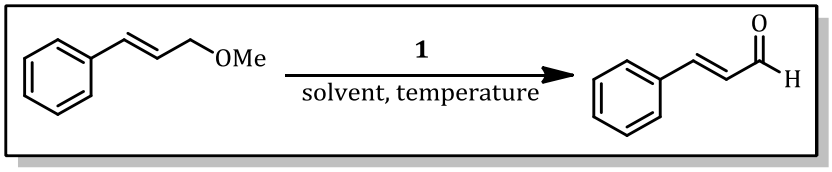
opportunity to probe the mechanism of Bobbitt's salt oxidations, which up until this point was still quite elusive. Our group had speculated that the oxidation occurs via a hydride transfer from the substrate to the oxoammonium cation. Cycloheptatriene is a particularly good system for such a reaction because a hydride removal from the methylene carbon yields a highly stable, aromatic tropylium ion. Additionally, oxidation of this system rules out other possible mechanisms because there are no heteroatoms present to initial a single electron transfer reaction. This project was supported by both experimental work as well as computational studies.



Scheme 9 Oxidative Functionalization of Cycloheptatriene

Results and Discussion

Much of my personal contribution to the oxidative cleavage of allyl ethers project began in the earliest phases of the project when we tested various conditions with the hope of reaching the proof of concept stage. We could predict facile cleavage of the allyl ether to the corresponding carboxylic acid product, but our hope was to minimize this pathway in favor of the partial oxidation to the aldehyde. Preliminary studies as well as further optimization studies were performed on the system shown in Scheme 10.



Scheme 10 Selected system for optimization studies

Initial optimization studies focused on reducing the carboxylic acid side product, first by screening various solvent mixtures. We had previously determined that the aqueous phase was essential for the cleavage step, and so our screen focused on various biphasic systems. The aqueous phase had two purposes: one was to mediate the quantity of Bobbitt's salt in the organic phase which reduces the amount of over-oxidation, and the second was to remove the methanol byproduct from the solution, helping to push the reaction equilibrium forward. Screening began with ethereal solvents providing less than optimal yields. Acetone yielded multiple products, likely due to Michael-like side reactions. Dichloromethane gave

us our first promising result as no acid formation was observed. We next probed the DCM:water ratio, settling on an optimal ratio of 8:2. Optimization was furthered by heating the reaction to 45 ^{o}C and finally increasing the Bobbitt's salt loading to 2.1 equiv. and extending the reaction time to 12 hours.

Table 3 Optimization of oxidative cleavage of allyl ethers

Entry	Solvent[a]	Temp. (^{o}C)	1a (eq.)	Time (h)	3a (%)[b]
1	MeCN: H_2O (9:1)	rt	1.1	2	84
2	Acetone:H_2O (9:1)	rt	1.1	2	-
3	THF:H_2O (9:1)	rt	1.1	2	17
4	Et_2O:H_2O (9:1)	rt	1.1	2	trace
5	CH_2Cl_2: H_2O (9:1)	rt	1.1	2	28
6	CH_2Cl_2: H_2O (8:2)	rt	1.1	2	35
7	CH_2Cl_2: H_2O (7:3)	rt	1.1	2	32
8	CH_2Cl_2: H_2O (8:2)	45	1.1	2	68
9	CH_2Cl_2: H_2O (8:2)	45	1.1	4	66
10	CH_2Cl_2: H_2O (8:2)	45	2.1	12	100 (93)

Conditions unless otherwise noted: **2a** (0.5 mmol, 1 equiv), solvent (2.5 mL) [a] Solvent ratios are by volume [b] Values in parentheses indicates isolated yields, all other values are conversions by ^{1}H spectroscopy

With optimal conditions in hand we turned to exploring the substrate scope of the reaction. Our first group of substrates were various cinnamyl analogues of the substrate studied in the optimization phase. Electronic changes through the addition of electron withdrawing or donating groups had little effect on the yield of the reaction, but did have a marked effect on the rate of reaction. Specifically, the *p*-CF_3 analogue required a longer reaction time of 72 hours as well as an increase in Bobbitt's salt loading. When steric hindrance was introduced to the system through substitution on the methylene carbon active site, the yield of the reaction was not diminished; however, a reduction in rate was observed once again. The next step in scope exploration involved variation of the ethereal alkyl group. Both ethyl and isopropyl ethers were successful under the reaction conditions, but a phenyl substituted ether failed to react. This likely occurred due to an increase in energy of the intermediate due to electron delocalization into the aromatic ring. A similar phenomenon was seen when the ether group was an acetate. The reaction proved to be fairly robust when the aryl ring was distanced from the allyl ether, as well as when the ring was removed completely. One of the few substrates that was not compatible with the reaction conditions was heterocycle containing system, which saw reduced yield due to polymerization.

We concluded this study with an examination of the possible oxidation mechanism. Similar to the mechanism proposed by Bailey[19], the key step in the mechanism is the transfer of a hydride from the allyl ether to the electrophilic oxygen of the oxoammonium cation. Hydration of the oxonium ion gives a hemiacetal, whose keto-form leads to formation of the desired aldehyde.

Hoping to elucidate the oxidation mechanism further, we performed this work in conjunction with the aforementioned cycloheptatriene oxidation studies. Prior to beginning synthetic experimentation, our group utilized computational modeling to predict the feasibility of this oxidation. The results showed that oxidation to the tropylium ion was indeed possible as the activation barrier for hydride transfer was quite low.

With this information, we proceeded to experiment with conditions for oxidizing cycloheptatriene and found we could accomplish this transformation quite successfully using two equivalents of Bobbitt's salt and two equivalents of pyridine. The complete conversion to this ion was observed through a characteristic 1H NMR signal at 9.36. Unfortunately, isolation of the tetrafluoroborate salt proved to be difficult due to the similar physical properties of the tropylium and oxoammonium tetrafluoroborate salts.

Seeking an alternative approach, we looked into the feasibility of performing a tandem oxidation functionalization reaction. This type of reaction was previously developed by Conrow, wherein tropylium tetrafluoroborate was functionalized using pyridine and acetylacetone.[20] In addition to this report, we performed further computational calculations to confirm the viability of this transformation. While I participated in a collaborative summer at Stonehill College under Prof. Leon Tilley, I performed a series of optimization studies and was able to isolate the functionalized product in 80% yield. This experimental result is the strongest support to date for the hydride transfer model for oxoammonium salt oxidations.

With the success of the initial functionalization studies, we hoped to develop our results into a full synthetic method. As our first experiments were performed on a test (1 mmol) scale, we first attempted a scaled-up reaction of 5 mmol and were able to isolate the product in 76% yield. Our next goal was to perform the reaction with a variety of functionalization partners. The compounds we screened included both 1,3,-diketones as well as β-keto esters, which have a common acidic proton on the methylene between the two carbonyl groups (Figure 3). Unfortunately we were unable to repeat our previous success with a different carbon nucleophile. We then altered our approach by performing an activation step on our carbon nucleophile through the formation of a sodium enolate. This step involved the reaction of one of our dicarbonyl species with sodium metal, and the products could be isolated and stored for future use. Our prediction was that adding these pre-deprotonated species would facilitate a faster, more streamline reaction and allow for higher product yields. Unfortunately, we did not see consistent success with this method.

[20] Conrow, K.; *J. Am. Chem. Soc*., **1959**, *81*, 5461

After several months of experimentation we were unable to devise a protocol for cycloheptatriene functionalization; however, the positive results we garnered in the computational studies were valuable enough to bring us satisfaction with the project.

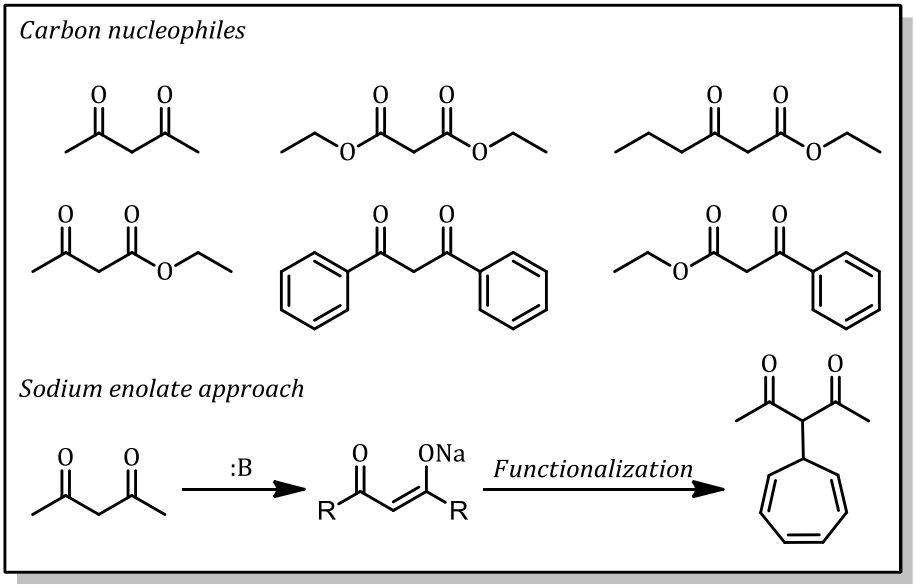


Figure 3 Carbon nucleophiles and their corresponding sodium enolates

Conclusions

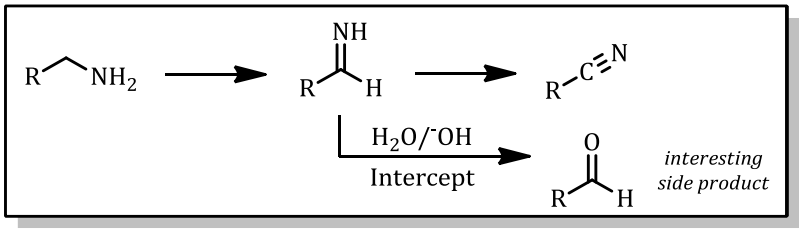
With the aim of further diversifying the utility of the oxoammonium salt Bobbitt's salt, we have developed a novel approach to oxidative cleavage of allyl ethers. The reaction occurs under mild conditions and with a broad substrate scope. High yield and ease of product isolation further show the utility of this transformation. Additionally, we have utilized studies of oxidative C-H functionalization of cycloheptratriene in combination with computational modeling to greatly enhance our understanding of the mechanism of oxoammonium salt oxidations.

2.3 Oxidative Deamination

Introduction

Taking oxoammonium salt oxidations in a new direction, the Leadbeater group and others have recently begun exploring the potential oxidations of amines. Recently the Bailey and Leadbeater groups co-developed a method for the oxidation of primary amines to

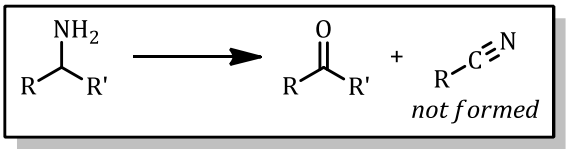
nitriles (Scheme 11).[21] Interestingly, while developing this protocol the groups discovered an interesting aldehyde side product. Optimization studies allowed for the obviation of this side reaction and complete conversion to the desired nitrile, but the aldehyde formation led to inspiration for a new oxidation method. In a further collaboration with the Bailey group, I participated in a project with the goal of oxidizing amines to their corresponding aldehydes. This transformation is not only synthetically useful, but also quite uncommon. There exist many methods for amination reactions of carbonyl species, but very few that can do the reverse. It was this high potential for synthetic utility that motivated us through the method development.



Scheme 11 Previous work and observation by the Bailey and Leadbeater groups

Results and Discussion

Initial optimization studies were guided toward selectively producing the aldehyde product. Unfortunately, we found it very difficult to eliminate the competing reaction of nitrile formation. In order to circumvent this issue, we decided to explore the oxidation of branched primary amines (Scheme 12). By exploiting the second R group of the branched amine, it is not possible to oxidize the amine to the nitrile, and hydrolysis to the corresponding ketone is the only available pathway.



Scheme 12 Primary Branched Amine Approach

Our first exploration into optimization studied 1-phenylethanamine with Bobbitt's salt in wet acetonitrile using sodium bicarbonate as the base. Unfortunately these conditions gave inconsistent yields. We then changed the pH by using sodium carbonate as the base, but observed a number of different products including the desired ketone, the α-keto

[21] Kelly, C. B.; Lambert, K. M.; Mercadante, M. A.; Ovian, J. M.; Bailey, W. F.; Leadbeater, N. E.; *Angew. Chem. Int. Ed.,* **2015**, *54*, 4241

aldehyde, and an aldol condensation product. Sources of these issues include self-reaction of the ketone product as well as reaction of the ammonia byproduct with the salt.

While optimization studies were being performed, I played a large role in preparing substrates for future scope studies. I synthesized a number of substrates which included several electron poor and electron rich phenyl rings (Figure 4). Additional substrates will be synthesized once optimization is complete.

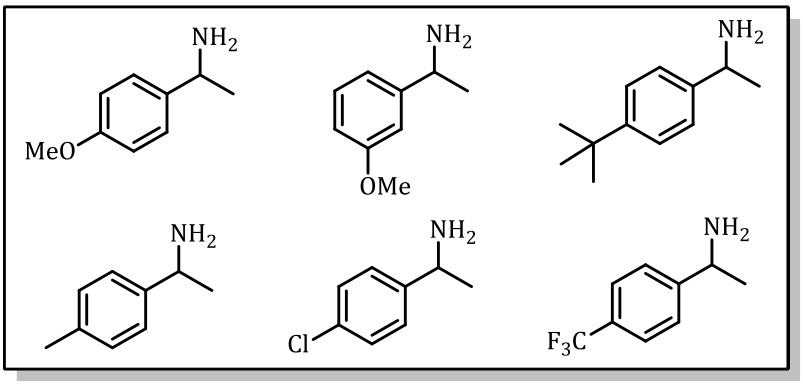
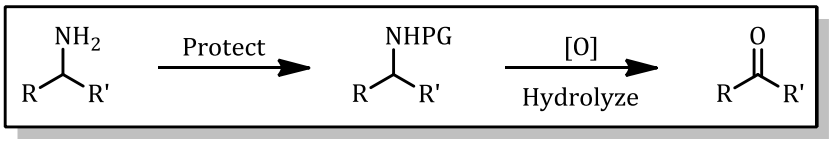


Figure 4 Substrates prepared for subsequent oxidative deamination

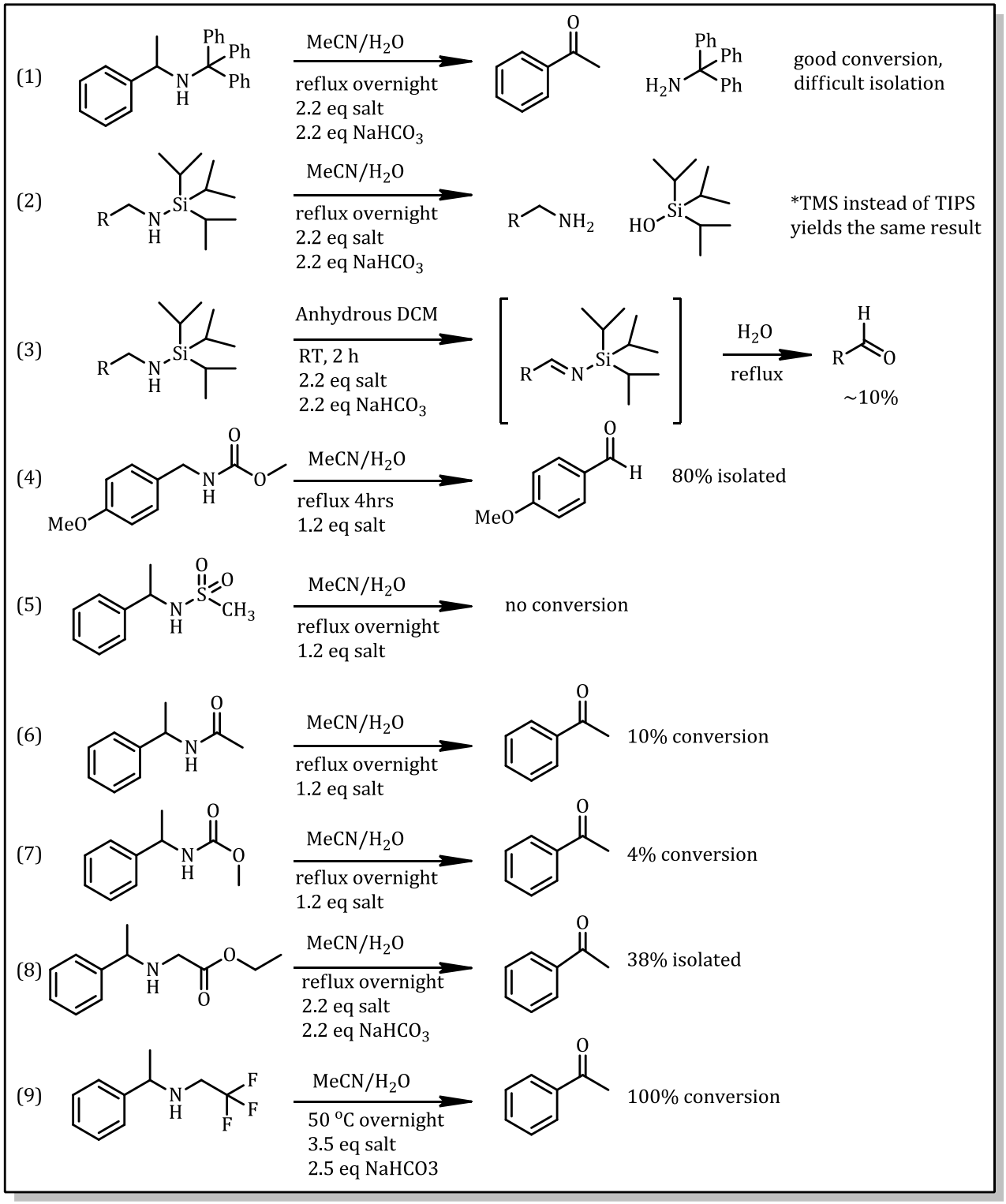
Still dissatisfied with our inconsistent yields, we changed our perspective and experimented with a completely new set of oxidation conditions. We proposed that oxidation could be more easily controlled by first protecting the amine because the reaction could be slowed in a precise manner (Scheme 13). Following protection, the amine would be hydrolyzed under normal conditions. We have explored a ride range of potential protecting groups, and have observed an equally wide range of results.



Scheme 13 Protecting group strategy

We first looked into various alkyl silyl protecting group hoping to slow the reaction through sterically blocking the active site. Both the trimethylsilyl and triisopropylsilyl groups (Scheme 14, Entries 2 and 3) could be added to the amine, but were too reactive to provide adequate protection as they spontaneously cleaved prior to the hydrolysis step. The trityl group (Scheme 14, Entry 1) was also a good candidate for steric blocking; however, even though good conversions were observed, isolation of the product proved too difficult for continued study. In an alternative approach to steric blocking, we also looked into protecting groups that would electronically slow the reaction by removing electron density from the reactive center. Our first test reaction protected the amine using

methylchloroformate to form the methyl carboxylate (Scheme 14, Entry 4). This protecting group provided high isolated yields, but only for unbranched primary amines.



Scheme 14 Optimization of protecting group strategy

We then tried a mesylate protecting group (Scheme 14, Entry 5) which failed for a few different reasons. First, the mesylate group is a fairly bulky species, and so the reaction was likely inhibited by steric interference. Second, the mesylate group may have been too electron withdrawing, slowing the reaction to the point where complete conversion is not observed. This idea was reinforced when several other protecting groups reacted too slowly to achieve ideal conversions (Scheme 14, Entries 6 and 7). To overcome this issue, we began examining protecting groups that removed the electron withdrawing moiety one methylene away from the amine. Our next test used an acetyl ethyl ester (Scheme 14, Entry 8) as the protecting group, which gave us a moderate increase in yield from 10% to 38%. Looking to continue this upward trend of isolated yield, our most recent experimentation looked into protection with a trifluoroethyl group (Scheme 14, Entry 9). We were thrilled to find that this system gave us 100% conversion. Following this result, our optimization studies are almost at their conclusion. The next step for this project is to continue synthesizing a diverse array of substrates to explore the scope of our conditions.

Conclusions

This project represents not only an interesting and unusual application of Bobbitt's salt oxidations, but it also exemplifies a remarkable feature of synthetic methods research. While developing a different method, the Bailey group was able to identify a competing side reaction and realize that the unwanted process could in itself be synthetically useful. Through my collaboration with the Bailey group, we have made great strides toward the completion of this method, and hope to have it fully developed in the coming months.

Chapter 3: Reimagining Fluoroform: From Greenhouse Gas to Chemical Workhorse

In the last several decades there has been an increase in global awareness about greenhouse gases and their connection to the growing concern of climate change. Greenhouses gases act as a buffer zone to prevent solar radiation from reflecting off the Earth's surface, instead trapping that energy in the atmosphere as heat. In the last century, the average global temperature has risen 2.7 °C almost entirely due to anthropogenic sources such as greenhouse gas emissions.[22]

Several developed countries have taken action to reduce greenhouse gas emissions by signing into law regulations that limit the production and emissions of these gases. Additionally, a standardized system known as the Global Warming Potential (GWP) has been established for determining the potency of each potentially harmful compound. GWP is a relative potency based on the lifetime of each molecule in the atmosphere as well as how efficiently it absorbs infrared radiation. Carbon dioxide, one of the most well-known greenhouse gases, has a GWP of 1 and is the standard to which other compounds are compared.

One specific greenhouse gas has caught the attention of several synthetic organic chemists and environmental chemists alike. Fluoroform (CHF_3) is the trifluorinated derivative of methane and has a GWP of about 12,000, meaning it is about five orders of magnitude more potent than CO_2.[23] As such, strict regulations have been implemented to control its release into the atmosphere. Fluoroform is produced on an industrial scale as the byproduct of the production of Teflon and other polymeric materials. As it is an undesired byproduct with limited applications, it is most commonly destroyed, usually by obliteration with plasma. This method is environmentally problematic because it can cause the production of hydrofluoric acid which is highly corrosive and acutely toxic.

Recently, fluoroform has gained the attention of synthetic chemists because of the increasing demand for organofluorine compounds and the potential use of fluoroform as a fluorine source. Much of the interest in fluorinated organic compounds stems from the unique steric and electronic properties of the trifluoromethyl (-CF_3) group. Notably, the presence of a –CF_3 group on a pharmaceutical product can greatly enhance the lipophilicity

[22] Hansen, J.; Ruedy, R.; Sato, M.; Lo. K; *Rev. Geophys.* **2010**, *48*, 4004

[23] Forster, P.; Ramaswamy, V.; Artaxo, P.; Berntsen, T.; Betts. R.; Fahey, D. W.; Haywood, J.; Lean, J.; Lowe, D. C.; Myhre, G.; Nganga, J.; Prinn, R.; Raga, G.; Schulz, M.; Van Dorland, R.; **2007**: Changes in Atmospheric Constituents and in Radiative Forcing. In: Climate Change 2007: The Physical Science Basis. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change [Solomon, S.; Qin, D.; Manning, M.; Chen, Z.; Marquis, M.; Averyt, K. B.; Tignor, M.; Miller,l, H. L. (eds.)]. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA.

of the drug, allowing for easier passage across the lipid bilayer of the cell.[24] The $-CF_3$ group also has the ability to serve as a bioisostere which has implications for the metabolic stability of the drug.

More specifically, an important functional group of interest is the trifluoromethyl ketone (TFMK). TFMKs have been proven to be potent enzyme inhibitors as well as important building blocks for the synthesis of $-CF_3$ containing heterocycles, such as Efavirenz (Figure 5).[25,26] Due to their growing popularity in pharmaceutical products, efforts have been made to increase the selection of available methods for TFMK synthesis.

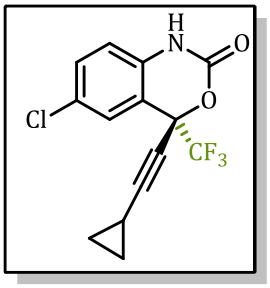


Figure 5 Efavirenz

Through the reimagination of fluoroform from an environmentally dreadful waste product to a useful synthetic reagent, we open many doors to the possibility of fluoroform as a $-CF_3$ source. The benefits of this change in perspective are two-fold: we would find both a utility for a previously unworkable gas as well as a novel method for TFMK synthesis.

The field of fluoroform activation was pioneered by Prakash and co-workers in 2012.[27] Their method features a base-mediated deprotonation of fluoroform by potassium bis(trimethylsilyl)amide (KHMDS). The activated fluoroform can them be reacted with a wide range of aldehydes, ketones, and esters. When followed by reaction with TMS-Cl, the product of the reaction is TMS-CF_3, which has come to be a widely used trifluoromethylating reagent (Scheme 15).[28]

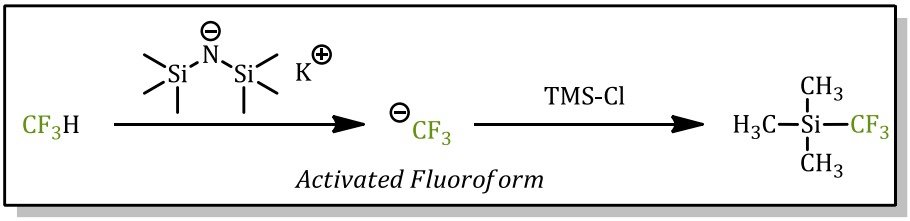
[24] *(a)* Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V.; *Chem. Soc. Rev.*, **2008**, *37*, 320 *(b)* Müller, C.; Faeh, C.; Diederich, C.; *Science*, **2007**, *3177*, 1881

[25] Gelb, M. H.; Svaren, J. P.; Abeles, R. H.; *Biochemistry*, **1985**, *24*, 1813

[26] Pierce, M. E.; Parsons Jr., R. L.; Radesca, L. A.; Lo, Y. S.; Silvermann, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; *J. Org. Chem.*, **1998**, *63*, 8563

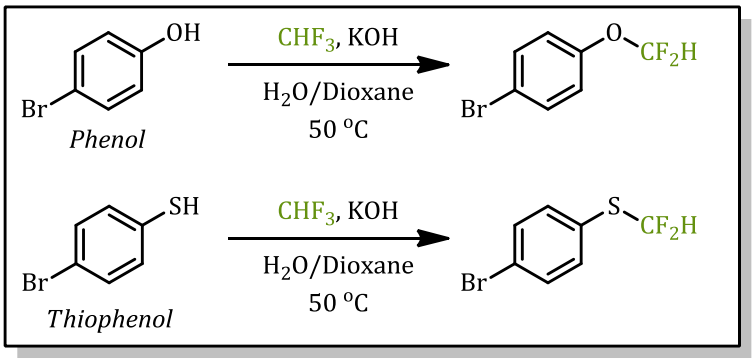
[27] Prakash, G. K. S.; Jog, P. V.; Batamack, P. T. D.; Olah, G. A.; *Science*, **2012**, *338*, 6112

[28] *(a)* Prakash, G. K. S.; Mandal, M.; *J. Fluorine Chem.*, **2001**, *112*, 123 *(b)* Prakash, G. K. S.; Yidin, A. K.; *Chem. Rev.*, **1997**, *97*, 757 *(c)* Gawronski, J.; Wascinska, N.; Gajewy, J.; *Chem. Rev.*, **2008**, *108*, 5227 *(d)* Singh, R. P.; Shreeve, J. M.; *Tetrahedron*, **2000**, *56*, 7613



Scheme 15 Prakash protocol for fluoroform activation

In a similar route to fluoroform fixation, Dolbier and co-workers developed a protocol for the fixation of fluoroform as difluorocarbene (:CF_2, a highly reactive species) followed by incorporation into organic molecules (Scheme 16).[29] This protocol utilizes potassium hydroxide (KOH) as the base and takes place in a biphasic solvent system of 1:1 water and dioxane.



Scheme 16 Dolbier protocol for activation to difluorocarbene

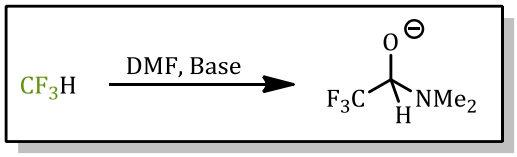
Fluoroform was also utilized to incorporate a difluoromethyl group in the protocol developed by Mikami, which features the difluoromethylation of lithium enolates (Scheme 17).[30]

Scheme 17 Mikami protocol for the difluoromethylation of lithium enolates

Another particularly interesting strategy was developed by Langlois which exploits the reactivity of fluoroform with DMF (Scheme 18)[31] He proposed that base deprotonation of fluoroform followed by addition of DMF would form a CF_3-DMF complex that would facilitate fast incorporation of fluoroform into other carbonyl species. Unfortunately, these methods

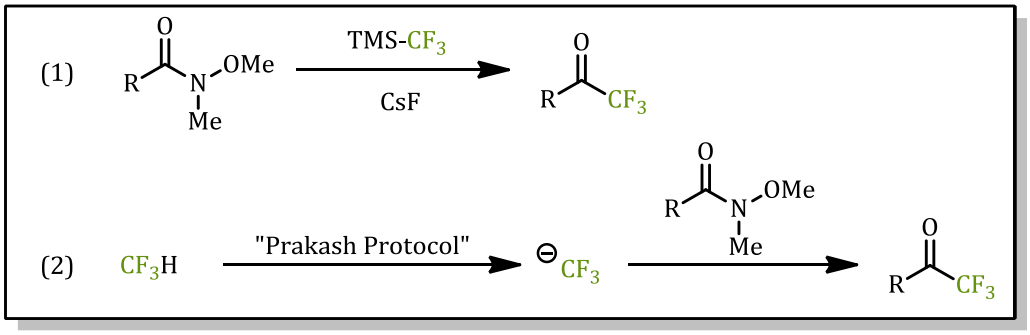
[29] Thomoson, C. S.; Dolbier, W. R.; *J. Org. Chem.*, **2013**, *78*, 8904
[30] Iida, T.; Hashimoto, R.; Aikawa, K.; Ito, S; Mikami, K; *Angew. Chem. Int. Ed.*, **2012**, *51*, 9535
[31] Large, S.; Roques, N.; Langlois, B. R.; *J. Org. Chem.*, **2000**, *65*, 8848

are limited by their inability to be scaled up, and therefore are not viable candidates for large-scale fluoroform utilization.



Scheme 18 Langlois activation with DMF

Seeking to develop a method for high-volume fluoroform utilization with high applicability to organic synthesis, we turned to previous work by the Leadbeater group for the synthesis of TFMKs (Scheme 19, Equation 1).[32] Specifically, we sought to transform Weinreb amides to TFMKs using activated fluoroform as an alternative -CF_3 source to TMS-CF_3 (Scheme 19, Equation 2). Not only is this an excellent application because it yields synthetically valuable products, but because TMS-CF_3 is itself produced from fluoroform, the route to TFMKs is simplified.[33]



Scheme 19 Preparations of TFMKs by (1) the Leadbeater group and (2) new method

[32] Rudzinski, D. M.; Kelly, C. B.; Leadbeater, N. E.; *Chem. Commun*. **2012**, *48*, 9610
[33] Trifluoromethyltrimethylsilane. *e-Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, **2010.**

Chapter 4: Fluoroform as a $-CF_3$ source

Results and Discussion

The first hurdle we faced with this project was devising a plan for how exactly we would carry out these reactions. Other than previous work by the Leadbeater group using continuous flow processing methods, we had limited experience in working with gaseous reagents. Additionally, fluoroform gas was a rather difficult material to acquire. This is due in part to the limited demand of the gas, thus increasing the cost of shipping and tank preparation. The lengthy process to purchase fluoroform is also due to the strict regulations that exist around its transport due to its greenhouse gas potency.

Upon receiving our tank of fluoroform we spent several days experimenting with potential reaction setups, finally settling on a simple balloon approach (Figure 6). Initial studies were performed using a balloon to deliver the to the reaction flask as a fluoroform atmosphere; however, later in our optimization studies we altered this delivery approach, as will be discussed.

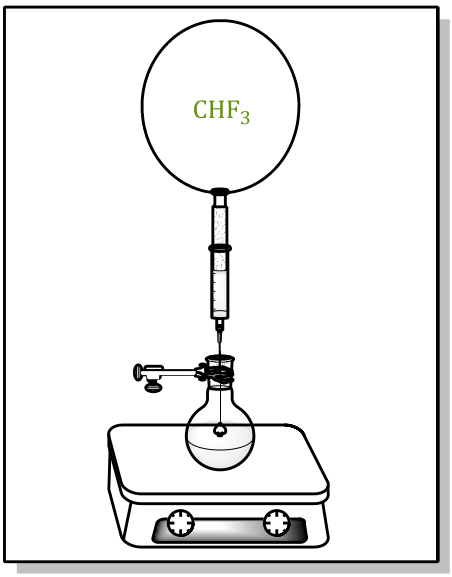
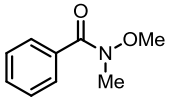
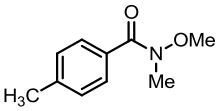
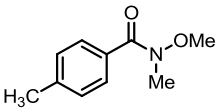
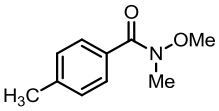
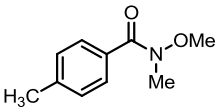
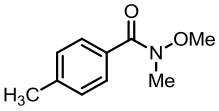
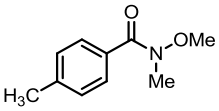
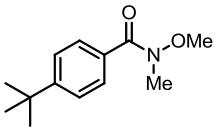
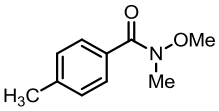
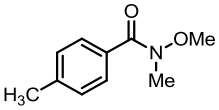
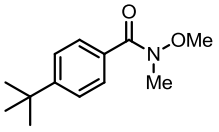
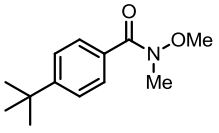
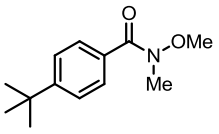
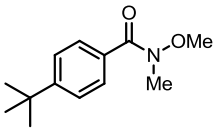
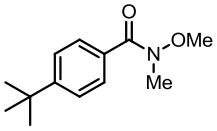
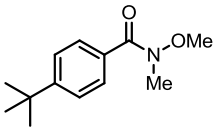
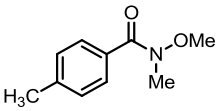
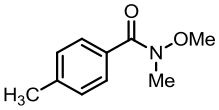


Figure 6 Fluoroform Balloon Setup

We first began our optimization studies by attempting to repeat the fluoroform incorporation procedures outlined in literature. Our first attempt was to test Prakash protocol conditions on a phenyl Weinreb amide (Table 4, Entry 1). This reaction featured deprotonation of fluoroform with KHMDS in toluene followed by addition of the amide. Unfortunately, we were unable to isolate our desired product after several attempts, including probing the order of addition of the reaction components (Table 4, Entry 2).

Table 4 Selected Fluoroform Incorporation Studies

Entry	Substrate	Base Conditions	CHF_3	Solvent	Goal	Result
1		KHMDS (BnH)	Atmosphere	Toluene, 0.3 M	Prakash Protocol	Mixed products
2		KHMDS (BnH)	Atmosphere	Toluene 0.3 M	Prakash order of addition	Mixed products
3		KHMDS (BnH), HMDS	Atmosphere, Bubbled In	DMF, 0.5 M	Langlois Protocol	Mixed products
4		KHMDS (BnH), HMDS	Atmosphere, Bubbled In	DMF, 0.5 M	Reduced Time	Mixed products
5		KHMDS (BnH), HMDS	Atmosphere, Bubbled In	DMF, 0.5 M	Longer Time	Slight exotherm
6		KHMDS (BnH), HMDS	Atmosphere, Bubbled In	DMF, 0.1 M	New CHF_3 Addition	30% conversion
7		KHMDS (BnH), HMDS	5 eq.	DMF, 10 mL	New CHF_3 Addition	50% conversion
8		KHMDS (THF), HMDS	5 eq.	DMF, 10 mL	New Base Solvent	555% ketone, 45% acid
9		KHMDS (THF), HMDS	5 eq.	DMF, 10 mL	Base Test	60% ketone, 40% amide
10		KHMDS (THF), HMDS	None	DMF, 10 mL	Primary Amide Formation	52% conversion to ketone
11		KHMDS (THF), HMDS	5 eq.	1:1 DMF:THF	Solvent Polarity	No Conversion
12		KHMDS (THF/Pentane) HMDS	5 eq.	DMF, 10 mL	Solvent Polarity	60% ketone
13		KHMDS (THF/pentane, 1.8 eq), HMDS	5 eq.	DMF, 10 mL	Increase Base	Incomplete conversion

14		KHMDS (THF/pentane, 1.3 eq.), HMDS	5 eq.	DMF, 10 mL	Slight Increase Base	Incomplete conversion
15		KHMDS (THF/pentane, 0.5 eq), HMDS	5 eq.	DMF, 10 mL	Substoichiometric Base	Incomplete conversion
16		KHMDS (THF/pentane) HMDS	5 eq.	DMF, 10 mL	Order of Addition	Incomplete conversion
17		KHMDS (MTBE/pentane) TMS-Tf	10 eq.	Toluene, 20 mL	TMF-TF	No Conversion
18		KHMDS (THF) CuCl	5 eq.	DMSO, 10 mL	Cu(I) Source	Incomplete conversion

We then began investigating Langlois conditions wherein the fluoroform is deprotonated and incorporated into the DMF solvent prior to addition of the substrate. Again, after several attempts and slight changes to the conditions, we were only able to obtain a mixture of products and starting material. We did see a slight increase in fluoroform solubility when DMF was used as the solvent, so the majority of our following test reactions continued using this solvent.

Following our initial examinations of the Langlois conditions, we decided to adjust our method of fluoroform addition (Entries 6 to 18). Previously, we were simply flushing the flask with fluoroform and then allowing a full balloon of gas to remain on the flask to maintain the fluoroform atmosphere. This setup limited our understanding of the reaction because we were unable to determine the amount of fluoroform dissolved in the solvent. To adjust for this issue, we began our experiments by preweighing a flask of solvent. A balloon of fluoroform was then bubbled into the solution for a pre-determined amount of time (usually ten minutes), and the final weight was taken to determine the amount of fluoroform added to the reaction mixture. From there, the proper equivalents and quantities of the other reagents was calculated. This method allowed more a more accurate understanding of the quantity of fluoroform available for reaction, but resulted in a marked decrease in reaction concentration.

We continued to screen a wide variety of reaction conditions, including solvent polarity, base conditions, and reaction times. Our solvent screen included a range of polarities, with nonpolar conditions including the introduction of pentane to the KHMDS solutions or using toluene as the primary solvent and polar conditions including using DMSO or KHMDS in THF. Our base conditions studies included those related to solvent polarity but also extended to the order of addition, reagent stoichiometry, and concentration. For

reaction time experimentation, we tested the reaction at as short as 1 hour to as long as several days. Unfortunately, none of the conditions we screened yielded preferential conversion to the TFMK or a high yield.

Given more time to devise optimal conditions, the next step of the method development would have been to prepare a range of electronically and sterically diverse Weinreb amides. If a broad scope were found, the method would be ready for publication. As a second portion of the project or as a future endeavor, we also saw the applicability of this reaction to continuous flow processing. This reaction would benefit from continuous flow processing for several reasons. First, the introduction of a gaseous reagent would become much more controlled and efficient, which is both more cost effective as well as environmentally conscious. Second, the use of continuous flow processing would bring us one step closer to performing this reaction on an industrial scale, which was the ultimate goal we pursued when designing this project.

Conclusions

While the conclusion of this project did not bring us a new synthetic method, there are still many valuable experiences that come from a failed project. Our optimization studies were extensive, and taught me how to take a problem and continue to look at it from different perspectives in order to try to learn more about the reaction. The field of fluoroform activation is still quite young in respect to the history of synthetic organic chemistry, so it is not unexpected for use to have hit roadblocks when there is so little precedence for this type of work. One of the biggest challenges of this project was being able to dissolve high enough quantities of fluoroform in solution to allow the reaction to occur. Further studies could be performed that involve a more sophisticated reaction set up or fluoroform introduction system, or perhaps increasing the pressure of the fluoroform atmosphere could incite more of the gas to dissolve. While my time working in the Leadbeater lab is coming to a close, this project still have many avenues left to explore should anyone choose to pursue them.

Experimental Data

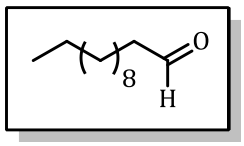
General:
All chemical transformations requiring inert atmospheric conditions or vacuum distillation utilized Schlenk line techniques with a 3- or 4-port dual-bank manifold. Nitrogen was used to provide such an atmosphere. NMR Spectra (^{1}H, ^{13}C, ^{19}F) were performed at 298 K on either a Brüker Avance Ultra Shield 300 MHz NMR, Brüker DRX-400 400 MHz NMR, or Brüker Avance 500 MHz NMR. ^{1}H-NMR Spectra obtained in $CDCl_3$ were referenced to residual non-deuterated chloroform (7.26 ppm) in the deuterated solvent. ^{13}C NMR Spectra obtained in $CDCl_3$ were referenced to chloroform (77.3 ppm). ^{19}F NMR spectra were referenced to hexafluorobenzene (-164.9 ppm).[34] Reactions were monitored by an Agilent Technologies 7820A Gas Chromatograph attached to a 5975 Mass Spectrometer, ^{1}H NMR, and/or by TLC on silica gel plates (60Å porosity, 250 μm thickness). High-resolution mass spectra were obtained using a JEOL AccuTOF-DART SVP 100 in positive direct analysis in real time (DART) ionization method, using PEG as the internal standard. TLC analysis was performed using hexanes/ethyl acetate as the eluent and visualized using permanganate stain, *p*-anisaldehyde stain, Seebach's Stain, and/or UV light. Flash chromatography and silica plugs utilized Dynamic Adsorbents Inc. Flash Silica Gel (60Å porosity, 32-63 μm).

Oxidative Esterification

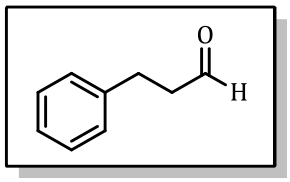
Chemicals:
Deuterated NMR solvents ($CDCl_3$) were purchased from Cambridge Isotope Laboratories. $CDCl_3$ was stored over 4Å molecular sieves and K_2CO_3. Pyridine was purchased from J. T. Baker (ACS Grade) and over 4Å molecular sieves. Sodium sulfate, sodium bicarbonate, THF (reagent grade), CH_2Cl_2, diethyl ether (ACS Grade and reagent grade) were purchased from Sigma-Aldrich. Aldehydes were either purchased from commercial suppliers (and distilled/recrystallized before use), or prepared in-house by procedures included in the manuscript. Hexafluorobenzene, HFIP, and TFE were purchased from Synquest Laboratories. The oxoammonium salt, 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, was prepared in-house according to the procedure outlined by Mercadante et al.[35]

[34] Ravikumar, I.; Saha, S.; Ghosh, P. Chem. Comm. **2011**, 47, 4721.
[35] Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E.; *Nat. Protoc.*, **2013**, *8*, 666

Preparation of Aldehyde Substrates



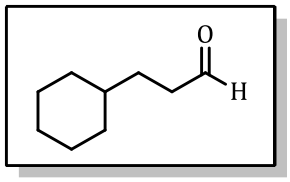
Dodecanal[36] To a 500 mL flask equipped with a stir bar was added 1-dodecanol (5.59 g, 30 mmol, 1 equiv) and DCM (183 mL, 0.1M in the alcohol). After mixing for a few minutes, the oxoammonium salt (5.76 g, 19.2 mmol, 1.05 equiv.) was added followed by 3.00 g of SiO_2 (1 mass equiv. to substrate). The flask was sealed with a rubber septa and the mixture was allowed to stir vigorously for 24 hours at room temperature. Upon reaction completion (confirmed by GC/MS analysis), the slurry was filtered solvent through Celite® *via* a coarse porosity fritted funnel. The solids were rinsed thoroughly with CH_2Cl_2 (≈ 300 mL). The filtrate was then adhered to silica gel by mixing it with 1.5 weight equivalents silica gel (relative to the theoretical yield, in this case ≈ 4.5 g) and removing the solvent *in vacuo* by rotary evaporation. A plug of silica was then assembled. This was done by adding 3-4 weight equivalents of silica (again relative to the theoretical yield) to a 60 mL coarse-porosity fritted glass funnel. An appropriately sized piece of filter paper relative to the size of the funnel was used to the top of the dry silica gel layer and this layer was pre-wet with hexanes. The dry packed material was gentle added evenly atop the filter paper. Another piece of appropriately sized filter paper was added atop this layer. The plug was eluted with a 95:5 by volume mixture of Hex:EtOAc (2-3 column volumes). The solvent was removed *in vacuo* by rotary evaporation to afford the pure aldehyde (4.90 g, 89%) as a clear, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.90 (t, *J*=6.90 Hz, 3 H) 1.14 - 1.40 (m, 16 H) 1.65 (quin, *J*=7.10 Hz, 2 H) 2.44 (td, *J*=7.34, 1.71 Hz, 2 H) 9.79 (t, *J*=1.83 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 14.32 (CH_3) 22.33 (CH_2) 22.93 (CH_2) 29.42 (CH_2) 29.58 (CH_2) 29.62 (CH_2) 29.69 (CH_2) 29.84 (CH_2) 29.85 (CH_2) 32.16 (CH_2) 44.15 (CH_2) 202.88 (C) **GC-MS** (EI) 184 ([M]$^+$, 1%) 140 (17%) 110 (19%) 96 (42%) 85 (23%) 82 (73%) 71 (37%) 68 (51%) 57 (100%) 55 (76%) 43 (84%) 41 (91%).



3-Phenylpropanal[37] To a 250 mL round bottom flask equipped with a stir bar, was added 3-phenylpropan-1-ol (4.09 g, 30 mmol, 1 equiv.) and DCM (75 mL, 0.4 M to alcohol). The oxoammonium salt (1.08 g, 6 mmol, 0.2 equiv.) was added to the solution. While stirring, commercial bleach (6% w/w) (37.5 mL, 30 mmol, 1.0 equiv.) was added all at once where the solution turned from yellow to bright red color. The solution was allowed to stir vigorously at room temperature for 60 min and monitor by GC-MS to assure reaction completion. Once the reaction is complete, transfer the solution to a separatory funnel and dilute with 50 mL of deionized water and extract with DCM (3 X 50 mL). Combine the organic extractions and wash with 100 mL of brine and dry over sodium sulfate. Remove

[36] Lahiri, G. K.; Chowdhury, A. D.; Ray, R. *Chem. Commun.* **2012**, *48*, 5497
[37] Tunge, J. A.; Jana, R. *Org. Lett.* **2009**, *11*, 971

the solvent *in vacuo* by rotary evaporation to get the crude aldehyde. The crude alcohol was then adhered to silica gel by mixing it with 1.5 weight equivalents silica gel (relative to the theoretical yield, in this case ≈ 6 g), dissolving it in CH_2Cl_2 (50 mL) and removing the solvent *in vacuo* by rotary evaporation. A plug of silica was then assembled. This was done by adding 3-4 weight equivalents of silica (again relative to the theoretical yield) to a 150 mL coarse-porosity fritted glass funnel. An appropriately sized piece of filter paper relative to the size of the funnel was used to the top of the dry silica gel layer and this layer was pre-wet with hexanes. The dry packed material was gentle added evenly atop the filter paper. Another piece of appropriately sized filter paper was added atop this layer. The desired alcohol was eluted off the plug *via* a 95:5 by volume mixture of Hex:EtOAc (3 column volumes). The solvent was removed *in vacuo* by rotary evaporation to afford the pure aldehyde (2.21 g, 55%) as a clear, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 2.79 (t, *J*=8.00 Hz, 2 H) 2.97 (t, *J*=7.60 Hz, 2 H) 7.17 - 7.24 (m, 3 H) 7.30 (*apparent triplet*, *J*=7.00 Hz, 2 H) 9.83 (t, *J*=1.46 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 28.38 (CH_2) 45.54 (CH_2) 126.57 (CH) 128.56 (CH) 128.87 (CH) 140.61 (C) 201.80 (C) **GC-MS** (EI) 134 ($[M]^+$, 61%) 133 ($[M-1]^+$, 10%) 105 (33%) 103 (16%) 92 (72%) 91 (100%) 78 (47%) 65 (16%)



3-Cyclohexylpropanal[38] **(2r)** To a 250 mL round bottom flask equipped with a stir bar, was added 3-cyclohexylpropan-1-ol (3.135 g, 22 mmol, 1 equiv.) and DCM (75 mL, 0.4 M to alcohol). The oxoammonium salt (1.08 g, 6 mmol, 0.2 equiv.) was added to the solution. While stirring, commercial bleach (6% w/w) (37.5 mL, 30 mmol, 1.0 equiv.) was added all at once where the solution turned from yellow to bright red color. The solution was allowed to stir vigorously at room temperature for 60 min and monitor by GC-MS to assure reaction completion. Once the reaction is complete, transfer the solution to a separatory funnel and dilute with 50 mL of deionized water and extract with DCM (3 X 50 mL). Combine the organic extractions and wash with 100 mL of brine and dry over sodium sulfate. Remove the solvent *in vacuo* by rotary evaporation to get the crude aldehyde. The crude alcohol was then adhered to silica gel by mixing it with 1.5 weight equivalents silica gel (relative to the theoretical yield, in this case ≈ 6 g), dissolving it in CH_2Cl_2 (50 mL) and removing the solvent *in vacuo* by rotary evaporation. A plug of silica was then assembled. This was done by adding 3-4 weight equivalents of silica (again relative to the theoretical yield) to a 150 mL coarse-porosity fritted glass funnel. An appropriately sized piece of filter paper relative to the size of the funnel was used to the top of the dry silica gel layer and this layer was pre-wet with hexanes. The dry packed material was gentle added evenly atop the filter paper. Another piece of appropriately sized filter paper was added atop this layer. The desired alcohol was eluted off the plug *via* a 95:5 by volume mixture of Hex:EtOAc (3 column volumes). The solvent was removed *in vacuo* by rotary evaporation to

[38] Breit, B.; Kemme, S. T.; Smejkal, T. *Chem. Eur. J.* **2010**, *16*, 3423

afford the pure aldehyde (2.44 g, 79%) as a clear, colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 0.81 - 1.00 (m, 2 H) 1.09 - 1.34 (m, 4 H) 1.52 (q, *J*=7.80 Hz, 2 H) 1.60 - 1.81 (m, 5 H) 2.43 (td, *J*=7.40, 1.95 Hz, 2 H) 9.77 (t, *J*=1.85 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 26.44 (CH_2) 26.71 (CH_2) 29.61 (CH) 33.28 (CH_2) 37.43 (CH_2) 41.77 (CH_2) 203.33 (C) **GC-MS** (EI) 140 ($[M]^+$, 2%) 122 (19%) 96 (62%) 94 (25%) 83 (24%) 81 (100%) 69 (7%) 67 (52%) 55 (73%) 41 (40%)

General Procedures for Oxidative Esterification for Preparation of Hexafluoroisopropyl (HFIP) Esters

General Procedure A[39]: Oxidation with Spent Oxidant Recovery for Nonvolatile Substrates

To a one-neck 50 mL round bottom flask equipped with a stir bar was added the aldehyde, (5 mmol, 1 equiv), pyridine (5.04 g, 63.75 mmol, 12.75 equiv) and HFIP (2.52 g, 3 equiv). The mixture was allowed to stir at room temperature for approximately five minutes. At this time, the salt (3.75 g, 12.5 mmol, 2.5 equiv) was added all at once (***CAUTION***: mildly exothermic) and the flask was sealed with a rubber septum. The reaction mixture was stirred at room temperature and gradually turned red. Once the reaction was judged complete[40], the HFIP was removed *in vacuo* by rotary evaporation (≈ 15 mmHg, 37 °C water bath). To this thick residue was added pentane[41] (≈ 30 mL) causing immediate precipitation of the nitroxide. ***Note:*** *While in most cases immediate precipitation was observed, if it was not, the remainder of the workup followed* ***General Procedure C***. The heterogeneous solution was allowed to stir for five minutes and the solids were filtered off through a medium porosity fritted funnel washing with pentane (≈ 250 mL). The solids were saved and filtrate was transferred to a separatory funnel and washed with 0.5 M HCl twice (≈ 150 mL). The organic layer was washed with deionized water (≈ 150 mL) and brine (≈ 150 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* via rotary evaporation (100 mmHg, 37 °C water bath)[42], affording the pure ester.

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[39] Note that there is very little difference (<5%) yield between procedures A/B vs. C. In most cases procedure C was used as it was the fastest to perform. However, if one seeks to reclaim the spent oxidant and regenerate the oxoammonium salt, procedures A/B have been provided.

[40] Note that, it is likely that these reaction are completed much sooner (<1 hr) due to the rapid appearance a deep red coloration after addition of the oxoammonium salt. This coloration indicates the presence of the nitroxide, which likely means the reaction is complete. Unfortunately, monitoring by NMR is complicated by the presence of the nitroxide. Therefore it is recommended that the reaction is monitored by TLC or GC/MS to determine reaction progress.

[41] Hexanes can also be used

[42] Note it is ***imperative*** that higher pressures are used during rotary evaporation to ensure good yields. Many of the esters synthesized are highly volatile and can easily be lost during solvent removal at lower pressures.

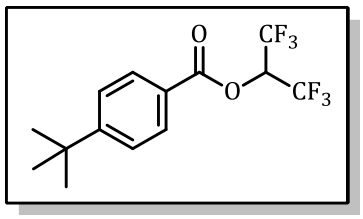
General Procedure B: Oxidation with Spent Oxidant Recovery for Volatile Substrates

To a one-neck 50 mL round bottom flask equipped with a stir bar was added the aldehyde (5 mmol, 1 equiv), pyridine (5.04 g, 63.75 mmol, 12.75 equiv) and HFIP (2.52 g, 3 equiv). The mixture was allowed to stir at room temperature for approximately five minutes. At this time, the salt (3.75 g, 12.5 mmol, 2.5 equiv) was added all at once (***CAUTION***: mildly exothermic) and the flask was sealed with a rubber septum. The reaction mixture was stirred at room temperature and gradually turned red. Once the reaction was judged complete, pentane (≈ 30 mL) was added to the reaction mixture causing immediate precipitation of the nitroxide. ***Note:*** *While in most cases immediate precipitation was observed, if it was not, the remainder of the workup followed* ***General Procedure C***. The heterogeneous solution was allowed to stir for five minutes and the solids were filtered off through a medium porosity fritted funnel washing with pentane (≈ 250 mL). The solids were saved and filtrate was transferred to a separatory funnel and washed with 0.5 M HCl twice (≈ 150 mL). The organic layer was washed with deionized water (≈ 150 mL) and brine (≈ 150 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* via rotary evaporation (100 mmHg, 37 ^oC water bath) affording the pure ester.

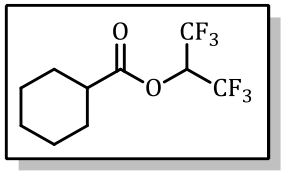
General Procedure C: Oxidation without Spent Oxidant Recovery

To a one-neck 50 mL round bottom flask equipped with a stir bar was added the aldehyde (5 mmol, 1 equiv), pyridine (5.04 g, 63.75 mmol, 12.75 equiv) and HFIP (2.52 g, 3 equiv). The mixture was allowed to stir at room temperature for approximately five minutes. At this time, the salt (3.75 g, 12.5 mmol, 2.5 equiv) was added all at once (***CAUTION***: mildly exothermic) and the flask was sealed with a rubber septum. The reaction mixture was stirred at room temperature and gradually turned red. Once the reaction was judged complete, pentane (≈ 30 mL) was added to the reaction mixture causing immediate precipitation of the nitroxide. The heterogeneous solution was allowed to stir for five minutes and the liquid was decanted into a separatory funnel. The solids were washed with pentane (3 X 40 mL). The solids were then dissolved in a 0.5 M HCl solution (≈ 40 mL) and transferred to the funnel. An additional ≈ 150 mL of a 0.5 M HCl was added. The layers were separated and the aqueous layer was extracted twice (≈ 2 X 75 mL). The combined organic layers were washed with deionized water (≈ 200 mL) and brine (≈ 200 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* via rotary evaporation (100 mmHg, 37 ^oC water bath) affording the pure ester.

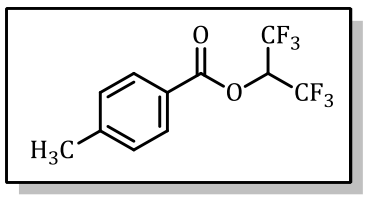
Preparation of Hexafluoroisopropyl (HFIP) Ester Substrates



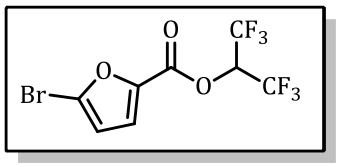
1,1,1,3,3,3-Hexafluoropropan-2-yl 4-(*tert*-butyl)benzoate (1.58 g, 96% yield) was prepared according to the representative procedure from 4-(*tert*-butyl)benzaldehyde (0.811 g, 5 mmol) as a clear, yellow liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.41 (s, 9 H) 6.10 (spt, J=6.00 Hz, 1 H) 7.59 (d, J=8.17 Hz, 2 H) 8.13 (d, J=7.98 Hz, 2 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 30.54 (CH_3) 34.88 (C) 66.43 (spt, $J_{C\text{-}C\text{-}F}$=34.50 Hz, CH) 120.30 (q, $J_{C\text{-}F}$=281.70 Hz, CF_3) 123.68 (C) 125.50 (CH) 130.07 (CH) 158.48 (C) 162.82 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.28 (d, J=5.45 Hz) **GC-MS** (EI) 328 ([M]$^+$, 9%) 313 (100%) 285 (37%) 161 (13%) 145 (10%) 118 (10%) 115 (10%) 91 (7%) 69 (5%) **HRMS** (ESI+) calcd for $C_{14}H_{15}F_6O_2$ [M$^+$]: 329.0976, found: 329.0947.



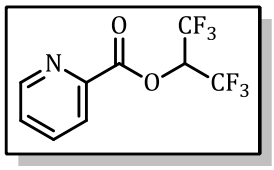
1,1,1,3,3,3-Hexafluoropropan-2-yl cyclohexanecarboxylate (1.04 g, 75%) was prepared according to the representative procedure from cyclohexanecarbaldehyde (0.5609 g, 5 mmol) as a clear, pale orange liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) □ ppm 1.25 - 1.41 (m, 3 H) 1.53 (*apparent quartet*, J=11.10 Hz, 2 H) 1.64 - 1.72 (m, 1 H) 1.74 - 1.85 (m, 2 H) 1.91 - 2.03 (m, 2 H) 2.54 (tt, J=11.30, 3.70 Hz, 1 H) 5.78 (spt, J=6.13 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) □ ppm 25.04 (CH_2) 25.46 (CH_2) 28.54 (CH_2) 42.34 (CH) 66.23 (spt, $J_{C\text{-}C\text{-}F}$ =34.50 Hz, CH) 120.55 (q, $J_{C\text{-}F}$ =284.60 Hz, CF_3) 172.54 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) □ ppm -124.55 (d, *J*=5.45 Hz) **GC-MS** (EI) 328 ([M]$^+$, 41%) 250 (9%) 223 (67%) 203 (11%) 183 (10%) 177 (13%) 111 (35%) 83 (90%) 69 (46%) 55 (100 %) 41 (43%) HRMS (ESI+) calcd for $C_{10}H_{13}F_6O_2$ [M$^+$]: 279.0820, found: 279.0819.



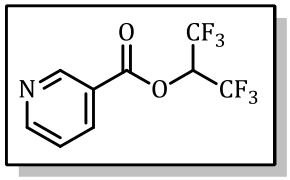
1,1,1,3,3,3-Hexafluoropropan-2-yl 4-methylbenzoate (1.35 g, 94%) was prepared according to the representative procedure from 4-methylbenzaldehyde (0.601 g, 5 mmol) as a clear, yellow liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 2.46 (s, 3 H) 6.08 (spt, J=6.20 Hz, 1 H) 7.32 (d, J=7.98 Hz, 2 H) 8.04 (d, J=8.17 Hz, 2 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 21.76 (CH_3) 66.98 (spt, $J_{C\text{-}C\text{-}F}$=34.80 Hz, CH) 120.87 (q, $J_{C\text{-}F}$=281.70 Hz, CF_3) 124.28 (C) 129.69 (CH) 130.66 (CH) 146.08 (C) 163.43 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.14 (d, J=5.45 Hz) **GC-MS** (EI) 286 ([M]$^+$, 35%) 119 (100%) 91 (39%) 89 (7%) 69 (8%) 65 (14%) **HRMS** (ESI+) calcd for $C_{11}H_9F_6O_2$ [M$^+$]: 287.0507, found: 287.0497.



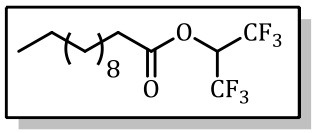
1,1,1,3,3,3-Hexafluoropropan-2-yl 5-bromofuran-2-carboxylate (1.55 g, 91%) was prepared according to the representative procedure from 5-bromofuran-2-carboxaldehyde (0.8749 g, 5 mmol) as a clear, light yellow liquid . **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 5.93 (spt, *J*=6.00 Hz, 1 H) 6.56 (d, *J*=3.50 Hz, 1 H) 7.36 (d, *J*=3.50 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 66.69 (spt, $J_{C\text{-}C\text{-}F}$ =34.50 Hz, CH) 114.79 (CH) 120.39 (q, $J_{C\text{-}F}$ =281.70 Hz, 16 C) 123.68 (CH) 130.85 (C) 143.04 (C) 153.79 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.18 (d, *J*=5.80 Hz) **GC-MS** (EI) 342 ($[M]^+$, ^{81}Br 7%) 340 ($[M]^+$, ^{79}Br 7%) 175 (^{81}Br 98%) 173 (^{79}Br 100%) 119 (^{81}Br 20%) 117 (^{79}Br 20%) 69 (27%) 66 (16%) 38 (19%) **HRMS** (ESI+) calcd for $C_8H_4BrF_6O_3$ [M^+]: 340.9248, found: 340.9255.



1,1,1,3,3,3-Hexafluoropropan-2-yl picolinate (1.20 g, 88%) was prepared according to the representative procedure from picolinaldehyde (0.536 g, 5 mmol) as a clear, yellow liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 6.00 (spt, J=6.00 Hz, 1 H) 7.49 (dd, J=7.01, 4.87 Hz, 1 H) 7.83 (t, J=7.49 Hz, 1 H) 8.09 (d, J=7.59 Hz, 1 H) 8.74 (d, J=3.89 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 67.13 (spt, $J_{C\text{-}C\text{-}F}$=34.50 Hz, CH) 120.17 (q, $J_{C\text{-}F}$=282.40 Hz, CF_3) 125.99 (CH) 127.97 (CH) 137.06 (CH) 144.79 (C) 150.36 (CH) 161.52 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -75.86 (d, J=5.45 Hz) **GC-MS** (EI) 273 ($[M]^+$, 3%) 107 (25%) 106 (31%) 79 (100%) 78 (91%) 69 (20%) 51 (28%) **HRMS** (ESI+) calcd for $C_9H_6F_6NO_2$ [M^+]: 274.0303, found: 274.0295.

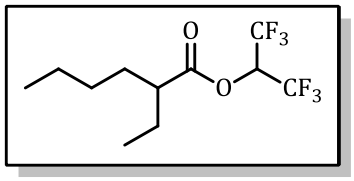


1,1,1,3,3,3-Hexafluoropropan-2-yl nicotinate (1.30 g, 95%) was prepared according to the representative procedure from nicotinaldehyde (0.536 g, 5 mmol) as a clear, yellow liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 6.06 (spt, J=5.80 Hz, 1 H) 7.41 (dd, J=6.81, 4.87 Hz, 1 H) 8.31 (d, J=7.40 Hz, 1 H) 8.82 (d, J=3.89 Hz, 1 H) 9.24 (s, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 66.45 (spt, $J_{C\text{-}C\text{-}F}$=34.50 Hz, CH) 119.79 (q, $J_{C\text{-}F}$=282.40 Hz, CF_3) 122.49 (CH) 123.00 (C) 137.04 (CH) 150.79 (CH) 154.37 (CH) 161.50 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.00 (d, J=5.45 Hz) **GC-MS** (EI) 273 ($[M]^+$, 69%) 106 (100%) 105 (12%) 78 (66%) 69 (17%) 51 (30%) **HRMS** (ESI+) calcd for $C_9H_6F_6NO_2$ [M^+]: 274.0303, found: 274.0283.

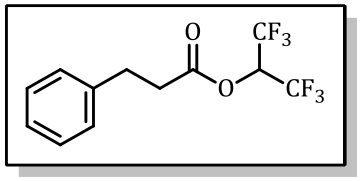


1,1,1,3,3,3-Hexafluoropropan-2-yl dodecanoate (1.38 g, 79%) was prepared according to the representative procedure from dodecanal (0.922 g, 5 mmol) as a clear, yellow liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 0.88 (t, J=6.80 Hz, 3 H) 1.22 - 1.39 (m, 16 H) 1.69 (quin, J=7.40 Hz, 2 H) 2.50 (t, J=7.40 Hz, 2 H) 5.77 (spt, J=6.20 Hz, 1 H) **^{13}C NMR**

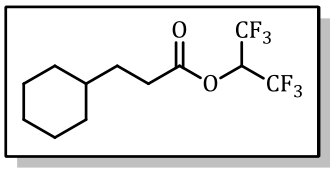
($CDCl_3$, 100 MHz) δ ppm 14.31 (CH_3) 23.00 (CH_2) 24.88 (CH_2) 29.11 (CH_2) 29.42 (CH_2) 29.65 (CH_2) 29.70 (CH_2) 29.86 (CH_2) 29.90 (CH_2) 32.24 (CH_2) 33.57 (CH_2) 66.62 (spt, $J_{C\text{-}C\text{-}F}$=34.50 Hz, CH) 120.82 (q, $J_{C\text{-}F}$=281.70 Hz, CF_3) 170.69 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.36 (t, J=8.20 Hz) **GC-MS** (EI) 351 ([M]$^+$, 9%) 350 (52%) 307 (32%) 279 (43%) 265 (20%) 251 (15%) 237 (27%) 223 (76%) 210 (68%) 203 (17%) 195 (20%) 183 (65%) 138 (44%) 97 (26%) 85 (45%) 83 (39%) 71 (48%) 69 (73%) 57 (79%) 55 (87%) 43 (100%) 41 (80%) **HRMS** (ESI+) calcd for $C_{15}H_{25}F_6O_2$ [M$^+$]: 351.1759, found: 351.1749.



1,1,1,3,3,3-Hexafluoropropan-2-yl 2-ethylhexanoate (1.272 g, 86%) was prepared according to the representative procedure from 2-ethylhexanal (0.641 g, 5 mmol) as a clear, light yellow liquid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 0.84 - 0.93 (m, 6 H) 1.18 - 1.37 (m, 4 H) 1.49 - 1.74 (m, 4 H) 2.49 (spt, *J*=4.70 Hz, 1 H) 5.80 (spt, *J*=6.10 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 11.32 (CH_3) 13.71 (CH_3) 22.40 (CH_2) 25.27 (CH_2) 29.15 (CH_2) 31.42 (CH_2) 46.85 (CH) 66.06 (spt, $J_{C\text{-}C\text{-}F}$ =35.20 Hz) 120.48 (q, $J_{C\text{-}F}$ =282.40 Hz, CF_3) 172.94 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.39 (d, *J*=5.45 Hz) **GC-MS** (EI) 294 ([M]$^+$, 1%) 266 (12%) 251 (20%) 238 (100%) 223 (92%) 203 (13%) 128 (10%) 69 (24%) 57 (35%) 55 (29%) 41 (26%) **HRMS** (ESI+) calcd for $C_{11}H_{17}F_6O_2$ [M$^+$]: 295.1133, found: 295.1127.

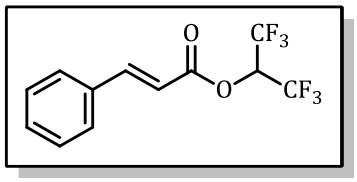


1,1,1,3,3,3-Hexafluoropropan-2-yl 3-phenylpropanoate (1.31 g, 87%) was prepared according to the representative procedure from 3-phenylpropanal (0.671 g, 5 mmol) as a clear, yellow liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 2.92 (t, J=7.40 Hz, 2 H) 3.11 (t, J=7.40 Hz, 2 H) 5.89 (spt, J=6.00 Hz, 1 H) 7.27 - 7.36 (m, 3 H) 7.37 - 7.44 (m, 2 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 30.17 (CH_2) 34.56 (CH_2) 66.26 (spt, $J_{C\text{-}C\text{-}F}$=34.50 Hz, CH) 120.20 (q, $J_{C\text{-}F}$=282.40 Hz, CF_3) 126.45 (CH) 127.92 (CH) 128.43 (CH) 138.92 (C) 169.35 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.25 (d, J=6.81 Hz) **GC-MS** (EI) 300 ([M]$^+$, 45%) 133 (11%) 105 (34) 104 (80%) 103 (15%) 91 (100%) 77 (19%) 69 (13%) 51 (10%) **HRMS** (ESI+) calcd for $C_{12}H_{10}F_6O_2$ [M$^+$]: 300.0585, found: 300.0609.

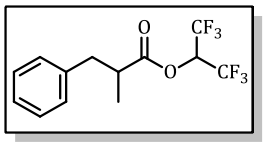


1,1,1,3,3,3-Hexafluoropropan-2-yl 3-cyclohexylpropanoate (1.03 g, 71%) was prepared according to the representative procedure from 3-cyclohexylpropanal (0.667 g, 4.76 mmol) as a clear, light yellow liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 0.94 (*apparent quartet*, *J*=11.70 Hz, 2 H) 1.18 - 1.31 (m, 4 H) 1.62 (q, J=7.60 Hz, 2 H) 1.74 (*apparent doublet*, *J*=9.93 Hz, 5 H) 2.55 (t, *J*=7.79 Hz, 2 H) 5.80 (spt, *J*=5.80 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 26.34 (CH_2) 30.95 (CH_2) 31.84 (CH) 32.80 (CH_2)

36.99 (CH_2) 66.31 (spt, $J_{C\text{-}C\text{-}F}$ =35.20 Hz, CH) 120.47 (q, $J_{C\text{-}F}$ =282.40 Hz, CF_3) 170.72 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.47 (d, J=2.73 Hz) **GC-MS** (EI) 306 ([M]$^+$, 1%) 288 (9%) 223 (11%) 139 (26%) 121 (32%) 110 (10%) 97 (72%) 96 (44%) 95 (22%) 83 (73%) 81 (42%) 69 (35%) 67 (30%) 55 (100%) 41 (40%) **HRMS** (ESI+) calcd for $C_{12}H_{17}F_6O_2$ [M$^+$]: 307.1133, found: 307.1136.



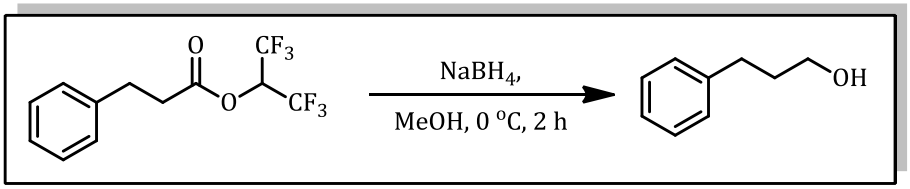
1,1,1,3,3,3-Hexafluoropropan-2-yl cinnamate (1.16 g, 78%) was prepared according to the representative procedure from cinnamaldehyde (0.661 g, 5 mmol) as a clear, yellow liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 6.01 (spt, J=6.20 Hz, 1 H) 6.52 (d, J=15.96 Hz, 1 H) 7.40 - 7.48 (m, 3 H) 7.56 (d, J=7.20 Hz, 2 H) 7.90 (d, J=15.96 Hz, 1 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 66.78 (spt, $J_{C\text{-}C\text{-}F}$=34.60 Hz, CH) 114.36 (CH) 120.95 (q, $J_{C\text{-}F}$=281.70 Hz, CF_3) 128.81 (CH) 129.26 (CH) 131.63 (CH) 133.75 (C) 149.48 (CH) 163.63 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.08 (d, J=6.81 Hz) **GC-MS** (EI) 298 (55%) 147 (8%) 131 (100%) 103 (54%) 77 (29%) 51 (13%) **HRMS** (ESI+) calcd for $C_{12}H_9F_6O_2$ [M$^+$]: 299.0507, found: 299.0481.



1,1,1,3,3,3-Hexafluoropropan-2-yl 2-methyl-3-phenylpropanoate (1.42 g, 90%) was prepared according to the representative procedure from 2-methyl-3-phenylpropanal (0.741 g, 5 mmol) as a clear, orange liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.31 (d, J=7.01 Hz, 3 H) 2.81 (dd, J=13.62, 7.59 Hz, 1 H) 3.02 (sxt, J=7.05 Hz, 1 H) 3.16 (dd, J=13.62, 7.01 Hz, 1 H) 5.81 (spt, J=6.10 Hz, 1 H) 7.23 (d, J=7.20 Hz, 2 H) 7.29 (t, J=6.80 Hz, 1 H) 7.36 (t, J=7.20 Hz, 2 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 16.34 (CH_3) 38.95 (CH) 40.84 (CH_2) 66.30 (spt, $J_{C\text{-}C\text{-}F}$ =34.50 Hz, 3 C) 120.32 (q, $J_{C\text{-}F}$ =289.00 Hz, CF_3) 126.64 (CH) 128.44 (CH) 128.74 (CH) 137.88 (C) 172.64 (C) **^{19}F NMR** ($CDCl_3$, 377 MHz) δ ppm -76.46 - -76.31 (m) **GC-MS** (EI) 314 ([M]$^+$, 18%) 147 (3%) 119 (7%) 117 (5%) 91 (100%) 69 (5%) 65 (6%) **HRMS** (ESI+) calcd for $C_{13}H_{12}F_6O_2$ [M$^+$]: 314.0741, found: 314.0741.

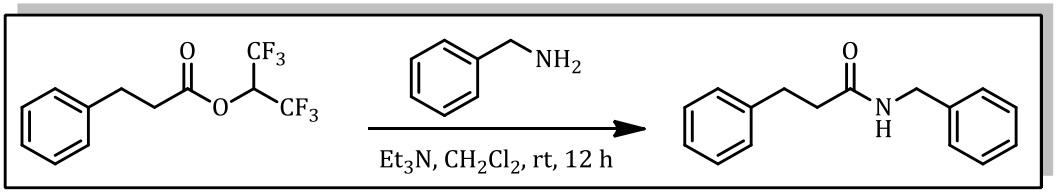
Synthesis of Carboxylic Acid Derivatives from Hexafluoroisopropyl Esters

Reduction with $NaBH_4$



3-Phenylpropan-1-ol[43] To a one-neck 250 mL round bottom flask equipped with a stir bar was added methanol (30 mL, 0.4 M in the ester) and the ester (2.10 g, 7 mmol, 1 equiv). The mixture was placed in an ice bath and allowed to cool while stirring for 10 minutes. At this time, sodium borohydride (1.33 g, 35 mmol, 5 equiv) was added very slowly portion wise. The reaction mixture was stirred at 0 °C for 2 hours. Once complete, the contents of the reaction flask were transferred to a separatory funnel and diluted with of deionized water (≈ 150 mL) and ether (≈ 150 mL). The aqueous layer was extracted with ether (2 X 100 mL). The organic layers were combined and washed with deionized water (≈ 100 mL) and brine (2 X 100 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation affording the pure alcohol (0.930 g, 98%) as a clear, colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 1.59 (br. s., 1 H) 1.93 (quin, *J*=7.30 Hz, 2 H) 2.74 (t, *J*=7.75 Hz, 2 H) 3.71 (t, *J*=6.20 Hz, 2 H) 7.24 (d, *J*=7.40 Hz, 3 H) 7.33 (t, *J*=7.40 Hz, 2 H) **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm 32.26 (CH_2) 34.44 (CH_2) 62.48 (CH_2) 126.09 (CH) 128.63 (CH) 128.67 (CH) 142.02 (C) **GC-MS** (EI) 136 ([M]$^+$, 22%) 118 (58%) 117 (100%) 105 (13%) 104 (13%) 92 (43%) 91 (89%) 77 (21%) 65 (16%) 51 (11%)

Amidation



***N*-Benzyl-3-phenylpropanamide**[44] To a one-neck 100 mL round bottom flask equipped with a stir bar was added the ester (1.80 g, 6 mmol, 1.0 equiv), triethylamine (0.668 g, 6.6 mmol, 1.1 equiv) and DCM (24 mL, 0.25 M in the ester). The mixture was allowed to stir at room temperature for approximately five minutes. At this time, benzyl amine (1.61 g, 15 mmol, 2.5 equiv) was added dropwise and the flask was sealed with a rubber septum. The reaction mixture was stirred at room temperature for 12 hours. Once complete, the contents of the reaction flask were transferred to a separatory funnel and diluted with 150 mL of DCM.

[43] Bodnar, B. S.; Vogt, P. F. *J. Org. Chem.* **2009**, *74*, 2598
[44] Kobayashi, S.; Soule, J. F.; Miyamura, H. *J. Am. Chem. Soc.* **2011**, *133*, 18550

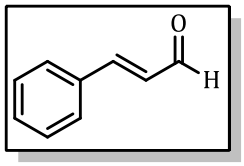
The organic layer was washed with 2 M HCl (3 X 100 mL) followed by 100 mL saturated aqueous $NaHCO_3$. The organic layer was washed with deionized water (≈ 150 mL) and brine (≈ 150 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation affording the pure amide (1.35 g, 94%) as a yellow powdery solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 2.54 (t, J=7.59 Hz, 2 H) 3.03 (t, J=7.59 Hz, 2 H) 4.43 (d, J=5.64 Hz, 2 H) 5.60 (br. s., 1 H) 7.14 - 7.20 (m, 2 H) 7.20 - 7.27 (m, 2 H) 7.27 - 7.35 (m, 6 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 32.02 (CH_2) 38.64 (CH_2) 43.76 (CH_2) 126.51 (CH) 127.66 (CH) 127.95 (CH) 128.66 (CH) 128.81 (CH) 128.90 (CH) 138.53 (C) 141.08 (C) 172.32 (C) **GC-MS** (EI) 240 ($[M+1]^+$, 16%) 239 ($[M]^+$, 87%) 148 (76%) 107 (50%) 105 (46%) 91 (100%) 79 (20%) 77 (24%) 65 (19%)

Cleavage of Allyl Ethers

Chemicals:

Deuterated NMR solvents ($CDCl_3$) were purchased from Cambridge Isotope Laboratories. $CDCl_3$ stored over 4Å molecular sieves and K_2CO_3. Sodium sulfate, sodium hydride, aluminum trichloride, sodium carbonate, THF (reagent grade), CH_2Cl_2, EtOH, Et_2O (ACS Grade and reagent grade), and TBAF (1 M in THF) were purchased from Sigma-Aldrich. Trifluoromethyltrimethylsilane and hexafluorobenzene were purchased from Synquest Laboratories and/or Oakwood Chemicals. Substituted propionic acid derivatives were either purchased commercially or prepared in house by Knoevenagel protocol from malonic acid and their corresponding aldehydes. [45] The oxoammonium salt 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidin-1-ium tetrafluoroborate was prepared according to our recently published protocol.[46]

General Oxidative Cleavage Protocol for Allyl Ethers



Cinnamaldehyde[47] To a 100 mL round bottom flask equipped with a stir bar was added the ether (0.010 mol, 1 equiv). CH_2Cl_2 (40 mL), and deionized water (10 mL). After stirring for five minutes, the oxoammonium salt (6.302 g, 0.021 mol, 2.1 equiv) was added to the flask and the flask was equipped with a reflux condenser. The flask was heated to 45 ^{o}C and allowed to stir overnight. The reaction mixture gradually became orange during this time. Reaction progress was monitored by GC/MS and/or ^{1}H NMR. After 12 h the

[45] See Hamlin, T. A.; Kelly, C. B.; Leadbeater, N. E. Eur. J. Org. Chem., **2013**, 3658 for a representative example of this protocol.
[46] Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E. *Nat. Protoc.* **2013**, *8*, 666.
[47] Park, C. P.; Kim, D.-P. *J. Am. Chem. Soc.*, **2010**, *132*, 10102.

reaction was judged to be complete.[48, 49, 50] At this time the reaction mixture was cooled to room temperature and transferred to a separatory funnel. The mixture was diluted with deionized water (100 mL) and Et_2O (150 mL) the layers were separated. The aqueous layer was extracted with Et_2O (5 × 50 mL). The combined organic layers were washed with deionized water (2 × 100 mL) and brine (150 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation to give the crude aldehyde. The crude aldehyde was then adhered to silica gel by mixing it with 1.5 weight equivalents silica gel (relative to the theoretical yield), dissolving it in CH_2Cl_2 and removing the solvent *in vacuo* by rotary evaporation. A plug of silica was then assembled. This was done by adding 3-4 weight equivalents of silica (again relative to the theoretical yield) to a 60 mL coarse-porosity fritted glass funnel. An appropriately sized piece of filter paper relative to the size of the funnel was used to the top of the dry silica gel layer. The dry packed material was gentle added evenly atop the filter paper. Another piece of appropriately sized filter paper was added over this layer. The desired aldehyde was eluted off the plug *via* a 95:5 by volume mixture of Hex:EtOAc (3 column volumes) followed by 9:1 by volume mixture of Hex:EtOAc (3 column volumes) . The solvent was removed *in vacuo* by rotary evaporation to afford the pure aldehyde.

Cycloheptatriene Functionalization

Chemicals:

Deuterated NMR solvents ($CDCl_3$, DMSO-d_6) were purchased from Cambridge Isotope Laboratories. $CDCl_3$ stored over 4Å molecular sieves. Magnesium turning. Na_2SO_4, MeOH, CH_2Cl_2, MeCN, Et_2O (ACS Grade and reagent grade), THF, pyridine, $NaBH_4$, $LiAlH_4$, NaH, acetic anhydride, $AlCl_3$, *p*-bromotoluene, (2-bromoethyl)benzene, cinnamyl alcohol, cycloheptatriene, acetylacetone, methyl iodide, and 1,1,3,3-tetramethylguanidinewere purchased from Sigma-Aldrich. Fluoroacetonitrile, 2,6-lutidine, and ethyl trifluoroacetate were purchased from Synquest Laboratories and/or Oakwood Chemicals. dimethyl methoxycarbonyl methanephosphonate was purchased from Alfa Aesar. Bleach (8.25 wt%) was purchased from Stop & Shop Supermarket Company. Alcohols used for relative rate

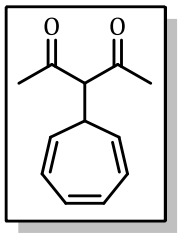
[48] The rate at which oxidative cleavage occurs dramatically varies between substrates. In several cases, we noted that the reaction would stall even after 24 h (usually at 90% conversion). To alleviate this, more **1a** was added (typically in 0.2 equiv intervals) and subsequently checked after 2 h. This process was repeated until complete or near complete cleavage was observed. Separation of aldehydes from their corresponding allyl ethers is difficult but can be accomplished using SiO_2 chromatography.

[49] If the reaction does stall and the goal is deprotection, it is advisable to simply carry the crude material to the reduction step

[50] We are unsure why in some cases the reaction stalls but we believe that it may relate to the oxoammonium salt function in two roles: One as a phase-transfer catalyst and one as the oxidant. Towards the end of the reaction, much of the oxidant is consumed in oxidation of the substrate and methanol thus limiting its ability to fulfill both roles. Another possibility is the competitive over-oxidation of methanol to CO_2 by way of formic acid.

studies were purchased from commercial suppliers. The oxoammonium salt 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidin-1-ium tetrafluoroborate was prepared according to our recently published protocol.[51]

General Procedure for Base-Promoted Functionalization



Tropylacetylacetone[52] To a 100 mL round bottom flask equipped with a stir bar was added Bobbitt's Salt (3.58 g, 0.01085 mol, 2.0 equiv) and MeCN (30 mL). The cycloheptatriene (0.50 g, 0.00543 mol, 1 equiv) was added dropwise to this solution. After four hours, the solution was checked for conversion by NMR. Once confirmed to be completely oxidized, acetylacetone (0.544 g, 0.00543 mol, 1 equiv) was added dropwise to the flask followed by pyridine (0.429 g, 0.00543 mol, 1 equiv). The reaction was allowed to stir overnight. After this time, the reaction was quenched with water (30 mL). The mixture was transferred to a separatory funnel. The aqueous layer was extracted a 7:3 by volume mixture of Hexanes:EtOAc (3 × 70 mL).[53] The combined organic layers were washed with 1 M HCl (2 × 50 mL) and brine (1 × 150 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed *in vacuo* by rotary evaporation to afford a pale yellow solid. This initial solid was washed with a minimal amount of pentane to afford the pure product (0.785 g, 76%) as a white solid. **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm 2.18 (s, 6 H) 2.92 (dt, *J*=11.35, 6.80 Hz, 1 H) 4.01 (d, *J*=11.35 Hz, 1 H) 5.18 (dd, *J*=9.31, 6.59 Hz, 2 H) 6.27 (dt, *J*=9.31, 3.07 Hz, 2 H) 6.71 (t, *J*=3.18 Hz, 2 H) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm 29.77 (CH_3) 38.38 (CH) 70.17 (CH) 122.14 (CH) 126.68 (CH) 131.39 (CH) 203.33 (C) **GC-MS** (EI) 194 ([M]$^+$, 0.1%) 147 (58%) 129 (15%) 105 (16%) 103 (11%) 91 (87%) 77 (18%) 65 (15%) 51 (11%) 43 (100%) 39 (11%)

General Procedure for Preparation of Sodium Enolates

To a 500 mL round bottom flask equipped with a stir bar was added the sodium metal (2.30 g, 100 mmol, 1 equiv.). The flask was sealed and flame dried, then placed under a N_2 atmosphere. To the flask was added dry ether (200 mL, 0.5 M in Na). The flask was equipped with an addition funnel kept under an N_2 atmosphere. The starting material (120 mmol, 1.2 equiv.) was diluted in dry ether (20 mL, 6 M in S.M.) and added to the addition funnel. The solution was added to the flask dropwise while stirring vigorously. Once addition was complete, the addition funnel was replaced with a reflux condenser. The flask was warmed to 35 °C and allowed to reflux overnight. After this time the flask was cooled to r.t. and the white solid product was filtered off. The solid was washed with 100 mL dry ether and 100 mL hexanes. The product was dried under the high vacuum to afford pure, dry product.

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[51] Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E. *Nat. Protoc.* **2013**, *8*, 666.
[52] Komatsu, K.; Tanaka, S.; Saito, S.; Okamoto, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3425.
[53] Based on solubility experiments, we found this to be the optimal solvent ratio for extraction that minimized impurity solubility (hydroxylamine of the salt, MeCN etc.) while maximized solubility of the desired product

General Procedure for Functionalization via Sodium Enolates

To a 100 mL round bottom flask equipped with a stir bar was added Bobbitt's salt (5.00 g, 16.5 mmol, 2 equiv.) and dissolved in MeCN (42 mL, 0.12 M). To the flask was added the cycloheptatriene (0.761 g, 8 mmol, 1 equiv.) and allowed to stir at r.t. for 5 minutes. To the reaction was added the sodium enolate (8 mmol, 1 equiv.) and allowed to stir at r. t. for 1 hour monitoring by ^{1}H NMR. Upon completion, the reaction was diluted with 30 mL ether and 30 mL deionized water. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted twice with 30 mL volumes of ether. The combined organic layers were washed twice with 30 mL volumes of 1 M HCl, once with 30 mL of saturated $NaHCO_3$, and once with brine. The solution was then dried with Na_2SO_4 and the solvent removed via rotary evaporation. The resulting crude material was purified using a silica gel plug and eluting with 8:2 hexanes:EtOAc to give the pure product as a yellow oil.

Oxidative Deamination

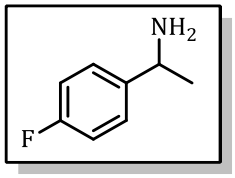
Chemicals:
Deuterated NMR solvents ($CDCl_3$) were purchased from Cambridge Isotope Laboratories. $CDCl_3$ stored over 4Å molecular sieves. Na_2SO_4, methanol, CH_2Cl_2, $NaBH_4$, $AlCl_3$, $NaBH_3CN$, 10% Pd/C, acetyl chloride, p-bromoacetophenone, p-methoxyacetophenone, p-chloroacetophenone, 1-napthylaldehyde $Ti(OiPr)_4$, NH_3 in EtOH,, 2-methyl-3-phenylacrylaldehyde, and *tert*-butylbenzene and 1,1,3,3-tetramethylguanidinewere purchased from Sigma-Aldrich. $Pd(OAc)_2$ was purchased from Oakwood Chemicals. M-methoxyacetophenone was purchased from Alfa Aesar. Ammonium Acetate was purchased from Mallinckrodt. Hydrogen gas (ultra high purity) was purchased from Airgas. Silica gel was purchased from Silicycle. *p*-Fluoroacetophenone was purchased from Eastman Chemicals. Bleach (8.25 wt%) was purchased from Stop & Shop Supermarket Company. The oxoammonium salt 4-acetamido-2,2,6,6-tetramethyl-1-oxopiperidin-1-ium tetrafluoroborate was prepared according to our recently published protocol. [54] 2,2,2-trifluoro-1-phenylethanone was prepared according to our recently published protocol.[55]

General Procedure for Reductive Amination by $NaBH_3CN$ and NH_4OAc

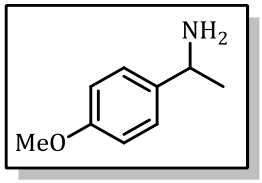
To a 100 mL round bottom flask was added the ketone (60 mmol, 1 equiv.) and dissolved in methanol (30 mL, 2 M). To the reaction was added the ammonium acetate (42.22 g, 548 mmol, 9.13 g, 9.13 equiv.) and slowly added the $NaBH_3CN$ (2.526 g, 40 mmol, 0.67 equiv.). The flask was equipped with an air condenser and the reaction was heated to 60 ^{o}C. The

[54] Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E. *Nat. Protoc.* **2013**, *8*, 666.
[55] Kelly, C. B.; Mercadante, M. A.; Hamlin, T. A.; Fletcher, M. H.; Leadbeater, N. E.; *J. Org. Chem.*, **2012**, *77*, 8131

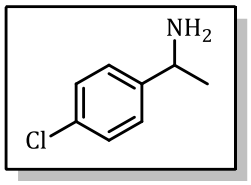
reaction was allowed to stir at 60 °C for 36 hours. If not complete as checked by NMR, an additional 0.4 equiv of $NaBH_3$ was added and the reaction was stirred an additional 24 horus at 60 °C.[56] After this time the solvent was removed via rotary evaporation to yield a thick residue. This residue was diluted with 30 mL of 6 M HCl, then transferred to a separatory funnel and further diluted with 100 mL of 6 M HCl. The layers were separated and the aqueous layer was washed with 4 volumes of 75 mL of DCM. The DCM can be discarded. The aqueous layer was basified using 6 M KOH until a pH of 14 was reached. The aqueous layer was extracted with 3 volumes of 100 mL of EtOAc. The combined organic layers were washed 1x with deionized water, 1x with brine, and then dried with Na_2SO_4. The solvent was removed in vacuo to afford the pure amine.



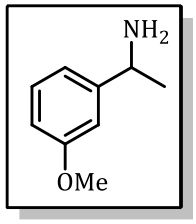
NO2-001 1-(4-fluorophenyl)ethanamine (1.3414 g, 48% yield) was prepared according to the representative procedure for reductive amination by $NaBH_3CN$ and NH_4OAc from *p*-fluoroacetophenone (2.763 g, 20 mmol) **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.28 (t, J = 7.1 Hz, 0.5 H) 1.38 (d, J = 6.6 Hz, 3 H) 4.14 (q, 6.6 Hz, 1H) 7.12 – 6.95 (m, 2 H) 7.42 – 7.30 (m, 2 H)



1-(4-methoxyphenyl)ethanamine (5.669 g, 63%) was prepared according to the representative procedure for reductive amination by $NaBH_3CN$ and NH_4OAc from *p*-methoxyacetophenone (9.610 g, 60 mmol) as a clear liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.39 (d, J = 6.6 Hz, 3 H) 1.53 (s, 2 H) 3.82 (s, 3 H) 4.21 – 4.06 (m, 1 H) 7.00 – 6.82 (m, 2 H) 7.29 (d, J = 8.5 Hz, 2 H)



1-(4-chlorophenyl)ethanamine was prepared according to the representative procedure for reductive amination by $NaBH_3CN$ and NH_4OAc from *p*-chloroacetophenone (6.184 g, 40 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.28 (t, J = 7.1 Hz, 1 H) 1.38 (d, J = 6.6 Hz, 3 H) 1.52 (d, J = 22.3 Hz, 2 H) 2.05 (s, 1 H) 4.14 (qd, J = 6.8, 4.7 Hz, 1 H) 7.28 (s, 4 H)

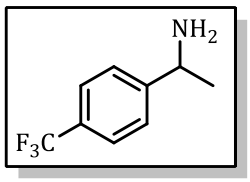


1-(3-methoxyphenyl)ethanamine (2.572 g, 43% yield) was prepared according to the representative procedure for reductive amination by $NaBH_3$ and NH_4OAc from *m*-methoxyacetophenone (6.007 g, 40 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm

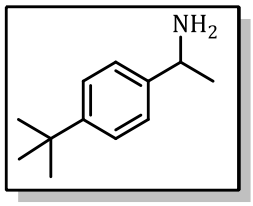
General Procedure for Reductive Amination by $Ti(iOPr)_4$ and NH_3

[56] Substrates requiring additional $NaBH_3$ will be noted in individual procedures

To a 100 mL round bottom flask was added the ketone (7 mmol, 1 equiv.), the $Ti(iOPr)_4$ (3.979 g, 14 mmol, 2 equiv.), and the NH_3 in EtOH (17.5 mL, 35 mmol, 5 equiv., 2 M in EtOH). The flask was capped with a septum and flushed with a nitrogen atmosphere. The reaction was allowed to stir at r.t. for 6 hours. After this time the septum was removed and the $NaBH_3CN$ (0.397 g, 10.5 mmol, 1.5 equiv.) was slowly added to flask. The reaction was allowed to stir open to air for an additional 3 hours. After this time the reaction as quenched with 25 mL of 2 M NH_4OH. The resulting precipitate was filtered off and washed with two 25 mL volumes of EtOAc. The resulting biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted once with 25 mL of EtOAc. The combined organic layers were extracted with 3 volumes of 30 mL of 1 M HCl. The combined aqueous layers were basified with 2 M KOH to a pH of 14. The base layer was extracted with 3 volumes of 50 mL of EtOAc. The combined organic layers were washed once with brine, then dried over Na_2SO_4. The solvent was removed in vacuo to afford the pure amine.



1-(4-(trifluoromethyl)phenyl)ethanamine (1.58 g, 42% yield) was prepared according to the representative procedure for reductive amination by $Ti(iOPr)_4$ and NH_3 from 1-(4-(trifluoromethyl)phenyl)ethanone (3.763 g, 20 mmol) as a pale yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.41 (d, 3 H) 1.53 (s, 2 H) 4.22 (q, 1 H) 7.60 (dd, 4 H)



1-(4-(tert-butyl)phenyl)ethanamine (0.613 g, 50% yield) was prepared according to the representative procedure for reductive amination by $Ti(iOPr)_4$ and NH_3 in EtOH from 1-(4-(tert-butyl)phenyl)ethanone (1.234 g, 7 mmol) as a clear liquid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm 1.34 (s, 9 H) 1.41 (d, J = 6.6 Hz, 3 H) 1.59 (d, J = 24.6 Hz, 2 H) 4.12 (q, J = 6.6 Hz, 1 H) 7.36 – 7.16 (m, 3 H) 7.48 – 7.36 (m, 2 H)

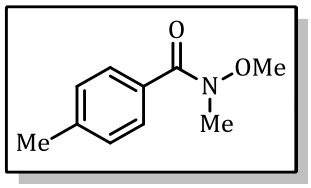
Fluoroform as a $-CF_3$ Source

Chemicals:

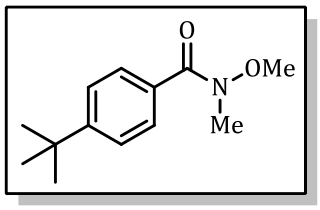
Deuterated NMR solvents ($CDCl_3$) were purchased from Cambridge Isotope Laboratories. $CDCl_3$ stored over 4Å molecular sieves. Na_2SO_4, CH_2Cl_2, DMF, toluene, THF, Et_2O (ACS Grade and reagent grade), hexanes, potassium bis(trimethylsilyl)azide (1.0 M in MTBE), potassium bis(trimethylsilyl)azide (0.5 M in toluene), *p*-methyltoluic acid, and *p*-*tert*-butyltoluic acid were purchased from Sigma-Aldrich. Hexamethyldisilazide was purchased from Oakwood Chemicals. Potassium bis(trimethylsilyl)azide (0.91 M in THF) was purchased from Alfa Aesar. Weinreb amides were synthesized according to our recently published protocol.

General Method for Weinreb Amide Preparation from Carboxylic Acids

To a 250 mL round bottom flask equipped with stir bar was added the carboxylic acid (25 mmol, 1 equiv) and DCM (80 mL ≈ 0.3M). To this stirred solution was added 1,1'-carbonyl diimadazole (4.46 g, 27.5 mmol, 1.1 equiv.) in one portion, turning the solution yellow and resulting in the evolution of CO_2 gas. The now yellow solution was allowed to stir for 45 minutes. At this time, N-O-dimethylhydroxylamine hydrochloride (2.68 g, 27.5 mmol, 1.1 equiv) was added all at once and the reaction mixture was stirred overnight. The reaction mixture was then quenched with 30 mL of 1 M HCl and stirred vigorously for 10 minutes. After this time, the solution was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with DCM (2 X 100 mL). The combine organic layers were washed with 1 M HCl (50 mL), deionized water (50 mL) and a 1:1 mixture of brine and a saturated sodium bicarbonate solution (100 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed in vacuo by rotary evaporation to afford the pure amide.



N-methoxy-N,4-dimethylbenzamide [57] (3.496 g, 78%) was synthesized from 4-methylbenzoic acid (3.404 g, 25 mmol) as a pure yellow oil. RW-NO1-185



4-(tert-butyl)-N-methoxy-N-methylbenzamide [56] (4.187 g, 76%) was synthesized from 4-*tert*-butylbenzoic acid (4.456 g, 25 mmol) as a pure yellow oil. RW-NO1-189

General Method A: Fluoroform Atmosphere Conditions

A 50 mL round bottom flask was flame dried and placed under a nitrogen atmosphere sealed with a rubber septum. To the flask was added dry DMF (10 mL) and the weinreb amide (5 mmol, 1 equiv). The flask was cooled to 0 °C and allowed to stir for ten minutes. A latex balloon was inflated with fluoroform. The balloon was inserted into the flask via a syringe needle through the septum, and the nitrogen atmosphere was flushed with fluoroform gas for sixty seconds. To the flask was added the KHMDS (5.5 mmol, 1.1 equiv) and HMDS (1 mmol, 0.2 equiv) successively. The flask was stirred at 0 °C for one hour, then slowly warmed to room temperature. The flask was allowed to stir at room temperature for five hours. After this time, the reaction was quenched with 10 mL 2N HCl and allowed to stir for ten minutes.

[57] Rudzinski, D. M.; Kelly, C. B.; Leadbeater, N. E.; *Chem. Commun.,* **2012**, *48*, 9610

The reaction mixture was transferred to a separatory funnel and the layers separated. The aqueous layer was extracted three times with ether. The combined organic layers were washed 1x with deionized water and 1x brine. The solution was dried over Na_2SO_4 and the solvent was removed via rotary evaporation to yield the crude product.

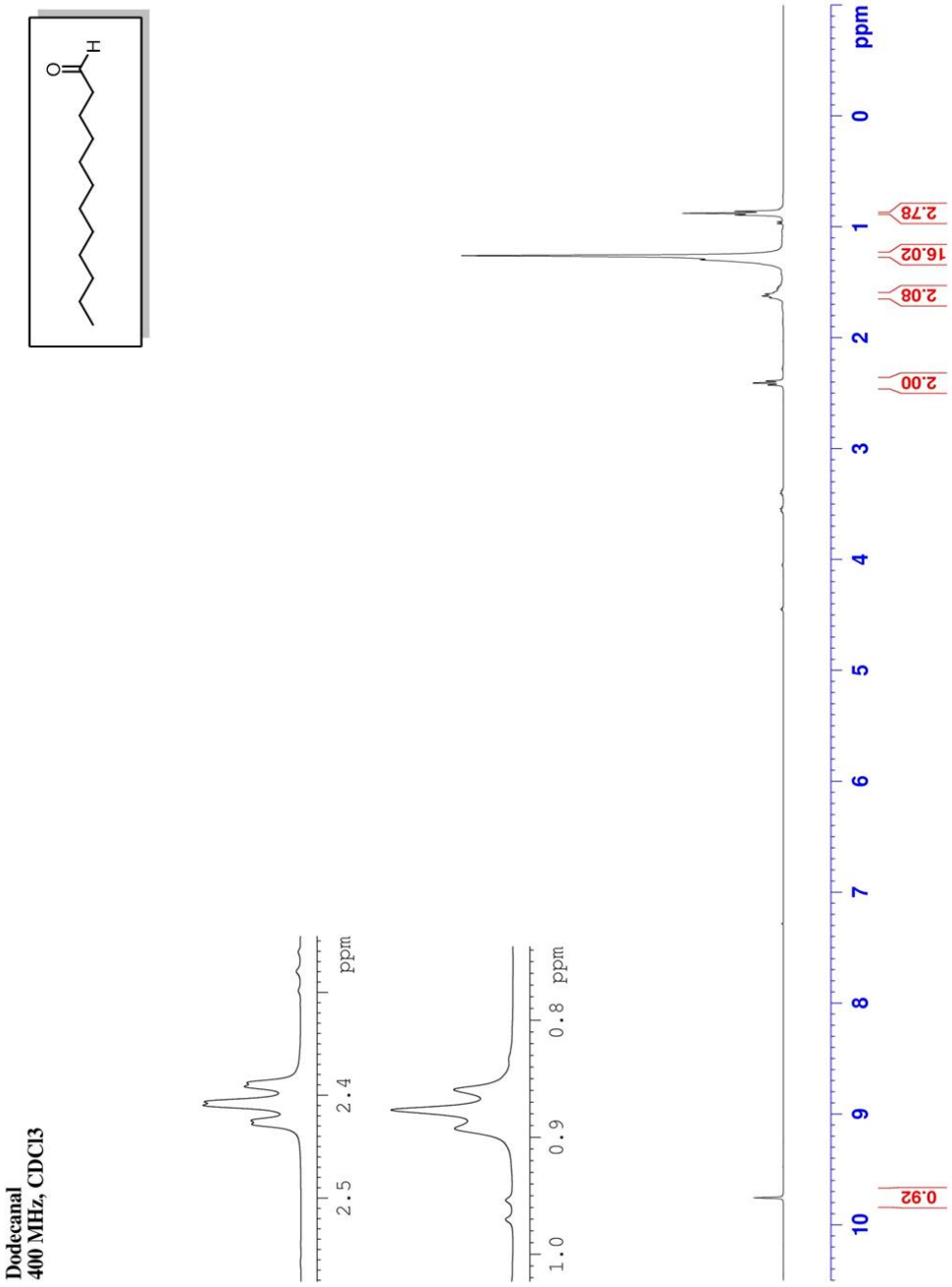
General Method B: Superstoichiometric Fluoroform Conditions

A 50 mL round bottom flask was flame dried and placed under a nitrogen atmosphere sealed with a rubber septum. To the flask was added dry DMF (10 mL) and the weight of the flask was taken. A latext balloon was inflated with fluoroform. The balloon was inserted into the flask via a 5" syringe needle through the septum, reaching below the level of the solvent. The balloon of fluoroform was bubbled in for ten minutes. After this time, the weight of the flask was taken again, and the mass of fluoroform added to the solution was determined (5 equiv of fluoroform). Using this quantity, the mass of Weinreb amide, KHMDS, and other reaction components was calculated. To the flask was added the Weinreb amide (5 mmol, 1 equiv). The reaction was cooled to 0 ^oC and allowed to stir for five minutes. To the flask was added the KHMDS (5.5 mmol, 1.1 equiv.) and HMDS (1 mmol, 0.2 equiv) successively. The flask was stirred at 0 ^oC for one hour, then slowly warmed to room temperature and allowed to stir for an additional five hours. After this time, the reaction was quenched with 10 mL 2N HCl and allowed to stir for ten minutes. The reaction mixture was transferred to a separatory funnel and the layers separated. The aqueous layer was extracted three times with ether. The combined organic layers were washed 1x with deionized water and 1x brine. The solution was dried over Na_2SO_4 and the solvent was removed via rotary evaporation to yield the crude product.

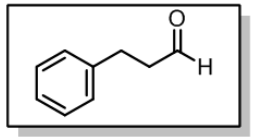
Spectra and Characterization

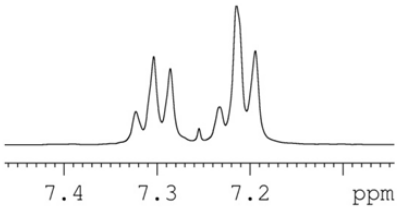
Oxidative Esterification

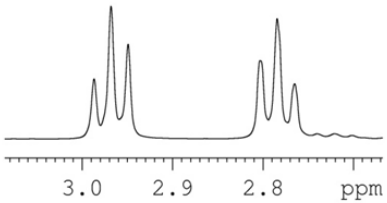
Preparation of Aldehyde Substrates

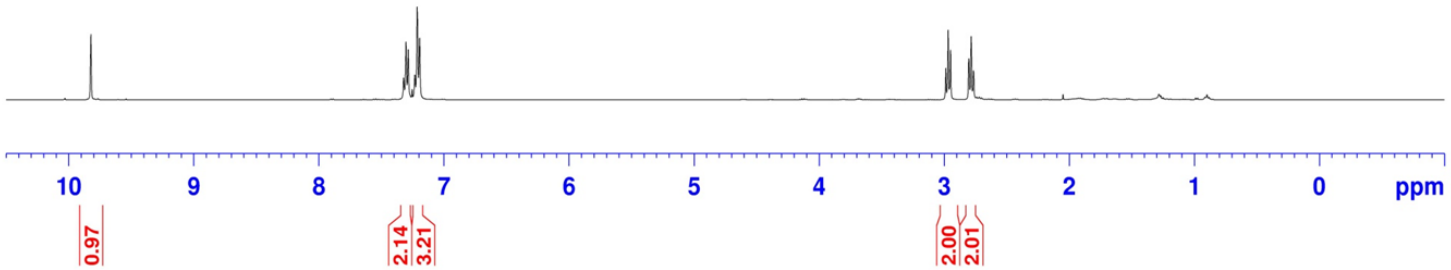


3–phenylpropanal
400 MHz, CDCl3

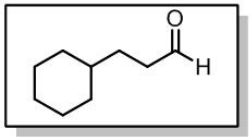


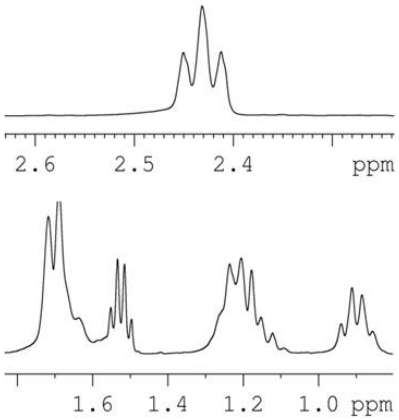


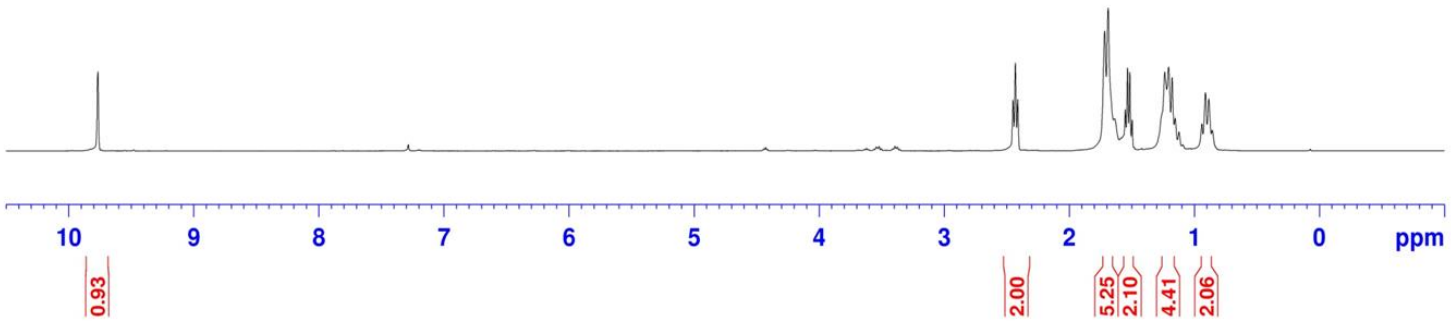




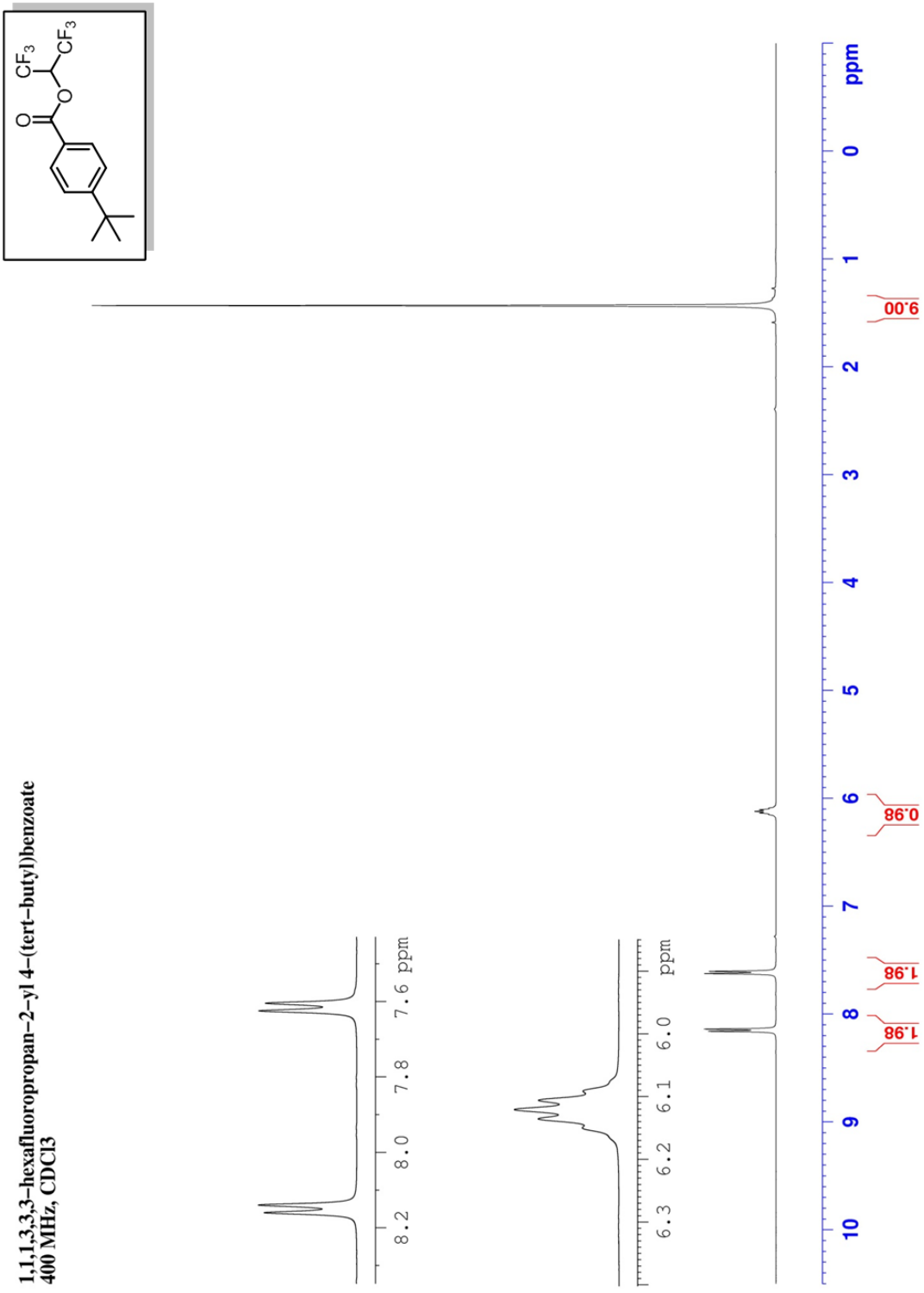
3−cyclohexylpropanal
400 MHz, CDCl3



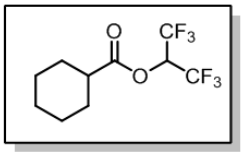


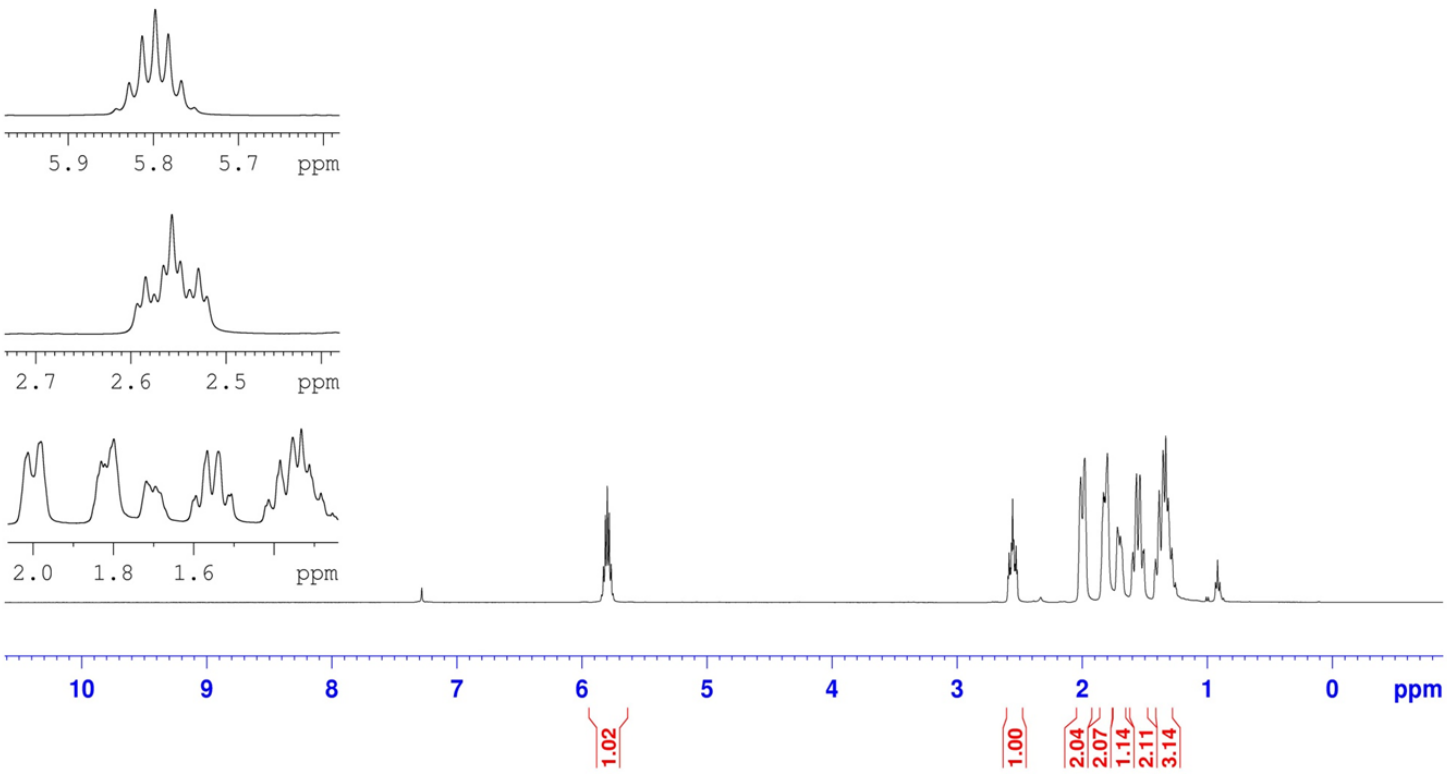


Preparation of Hexafluoroisopropyl (HFIP) Ester Substrates

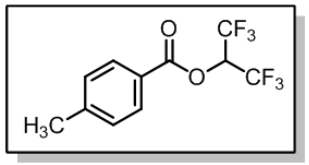


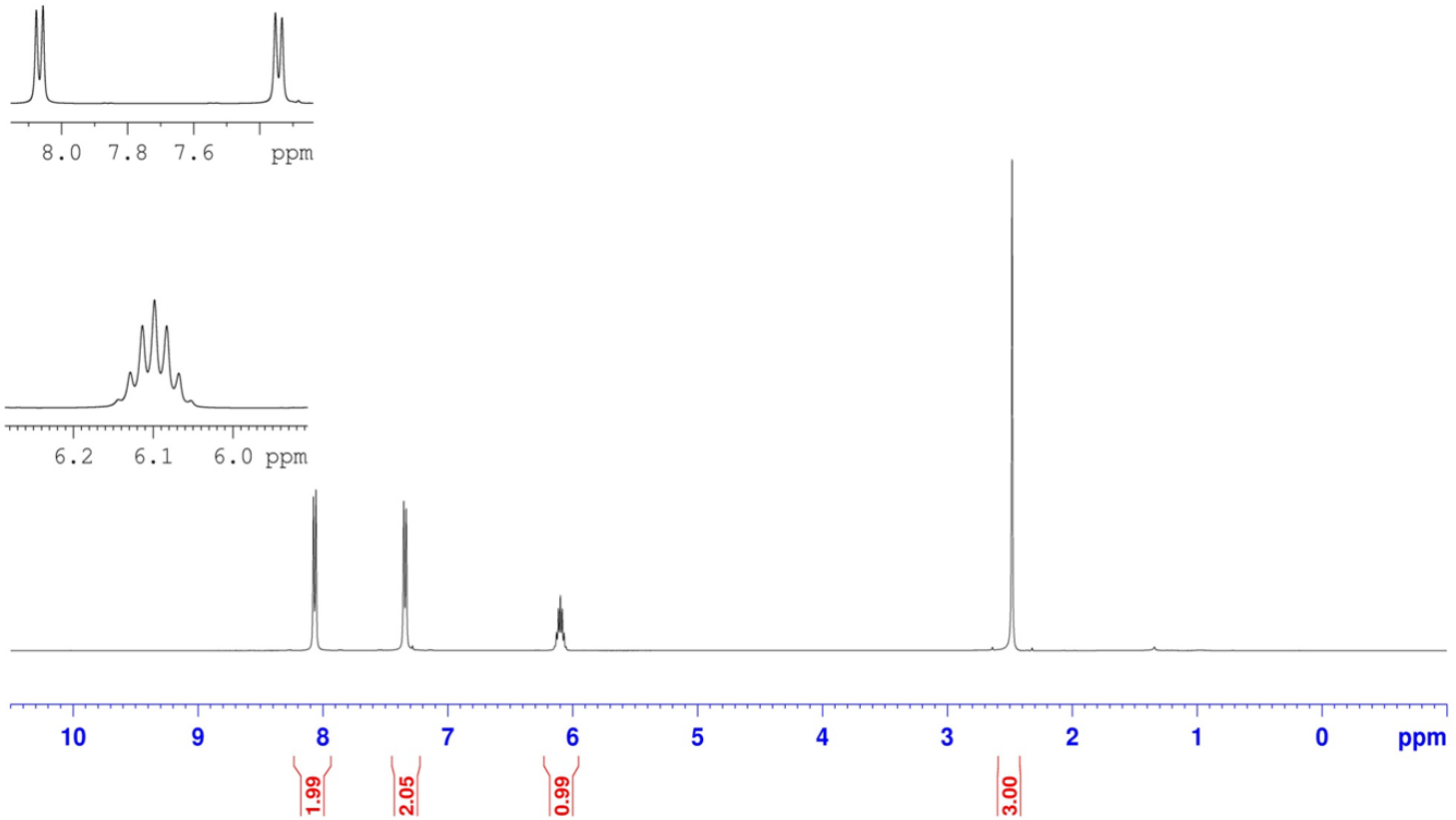
1,1,1,3,3,3−hexafluoropropan−2−yl cyclohexanecarboxylate
400 MHz, CDCl3



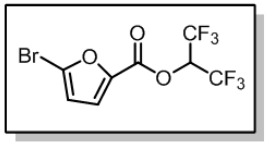


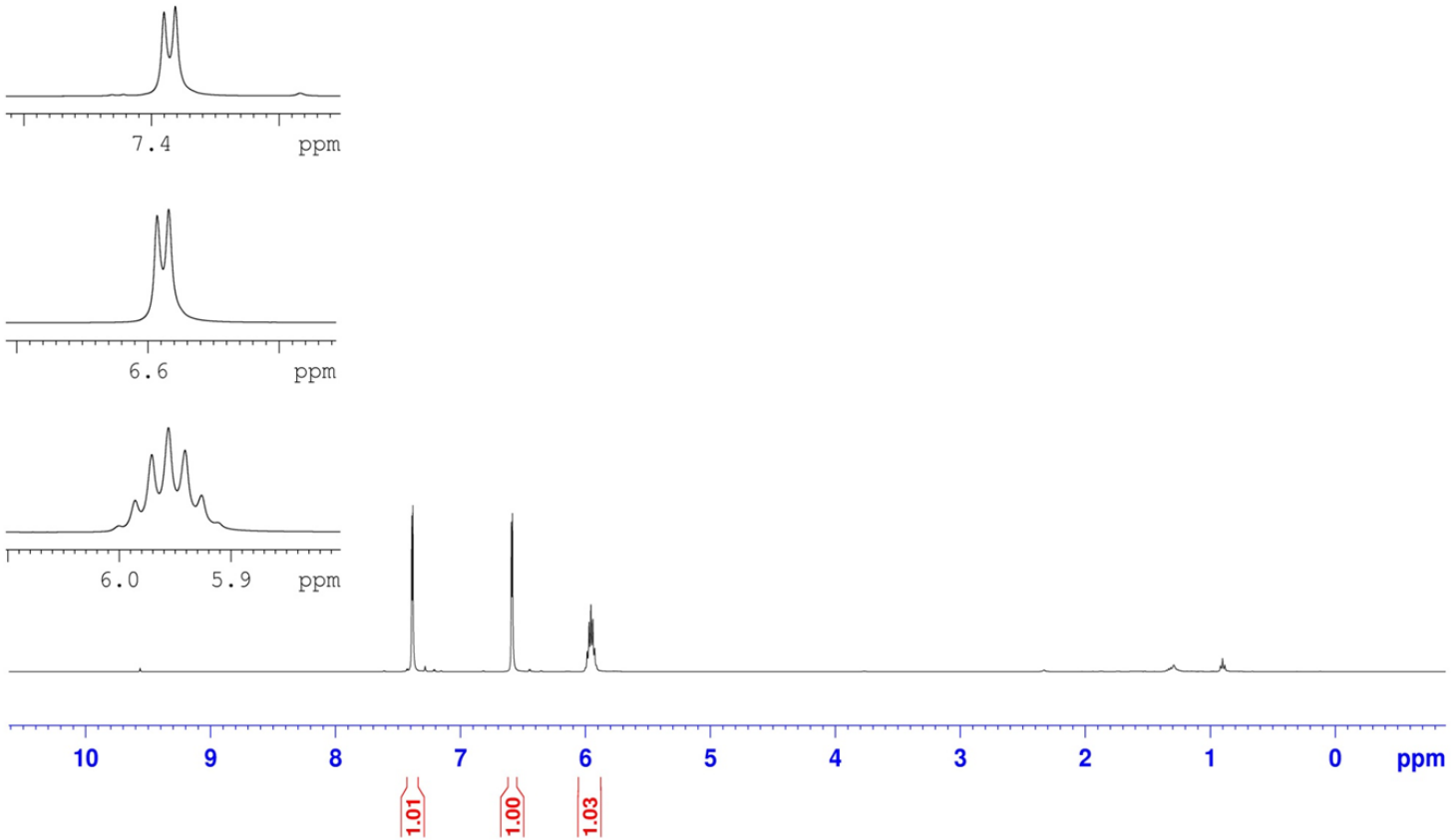
1,1,1,3,3,3–hexafluoropropan–2–yl 4–methylbenzoate
400 MHz, CDCl3



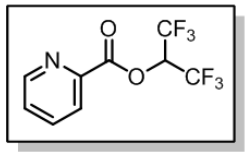


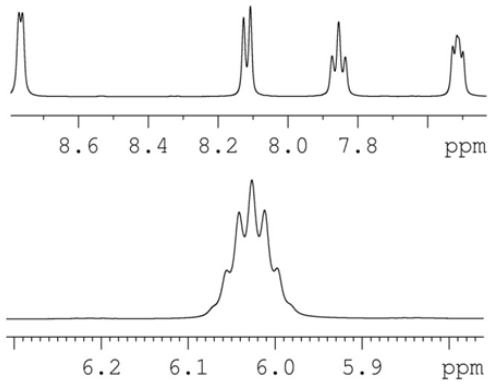
1,1,1,3,3,3–hexafluoropropan–2–yl 5–bromofuran–2–carboxylate
400 MHz, CDCl3

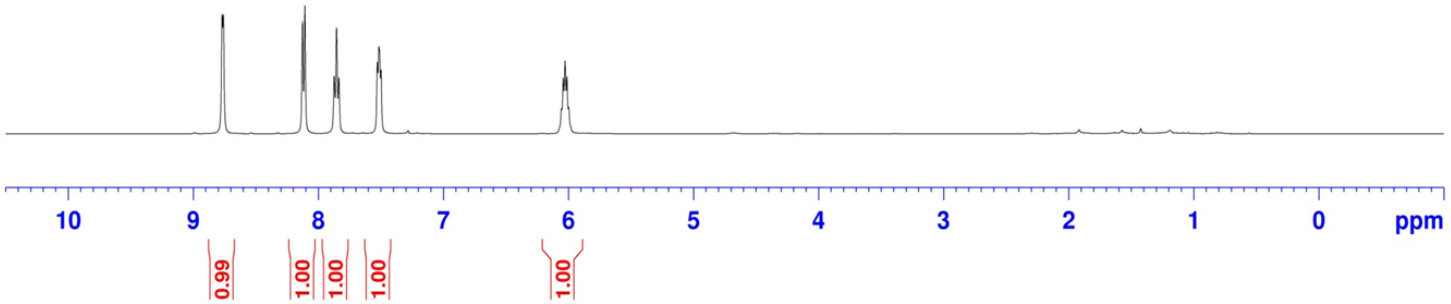




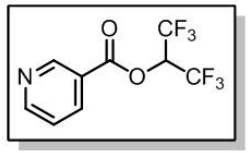
1,1,1,3,3,3–hexafluoropropan–2–yl picolinate
400 MHz, CDCl3

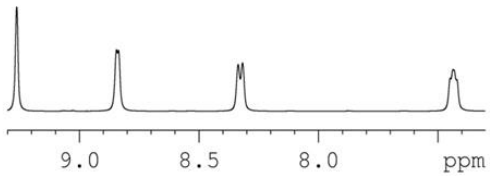


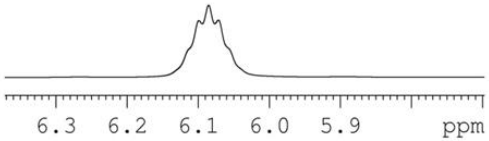


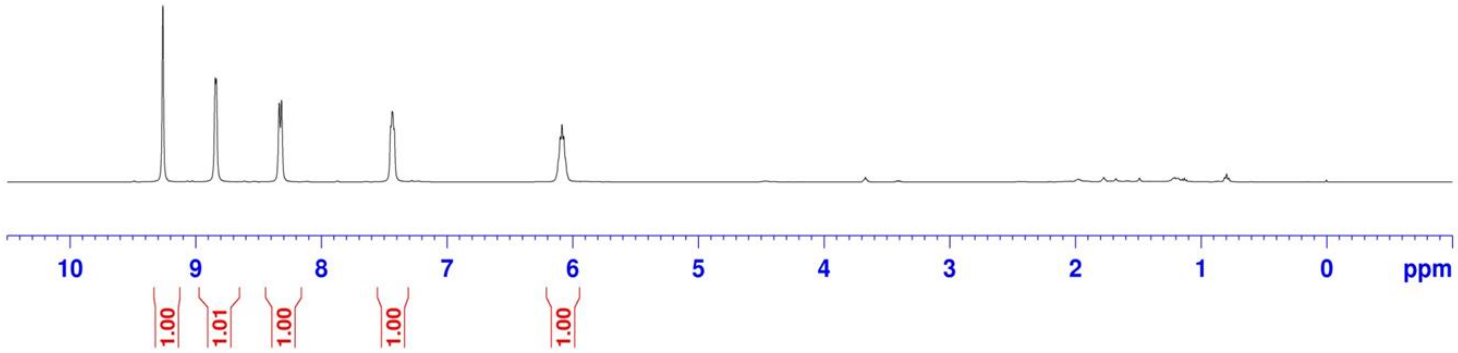


1,1,1,3,3,3–hexafluoropropan–2–yl nicotinate
400 MHz, CDCl3

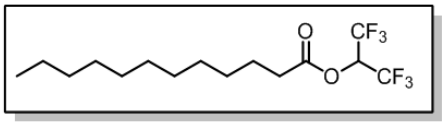


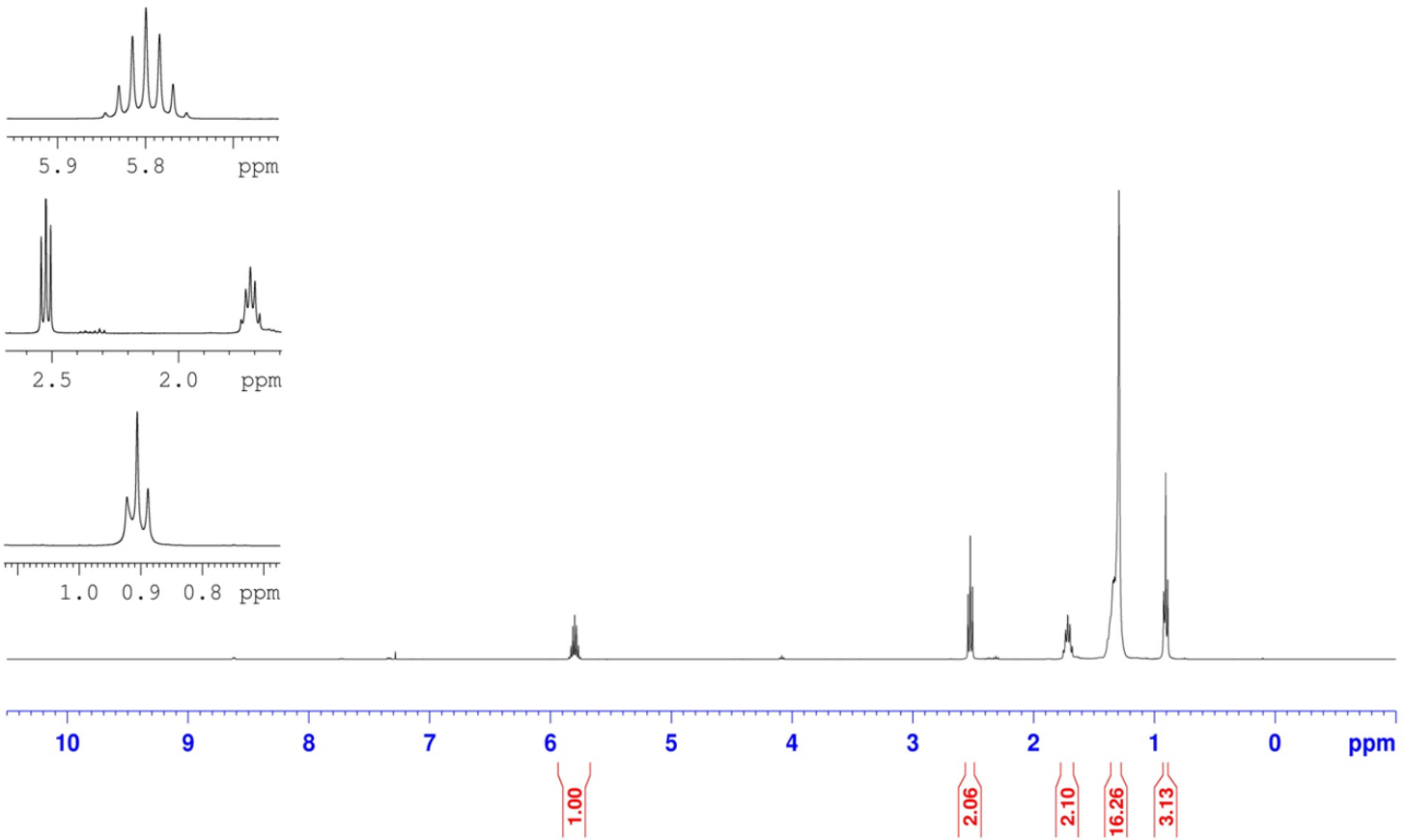




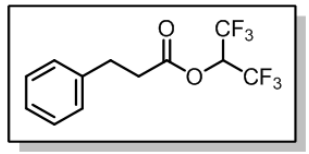


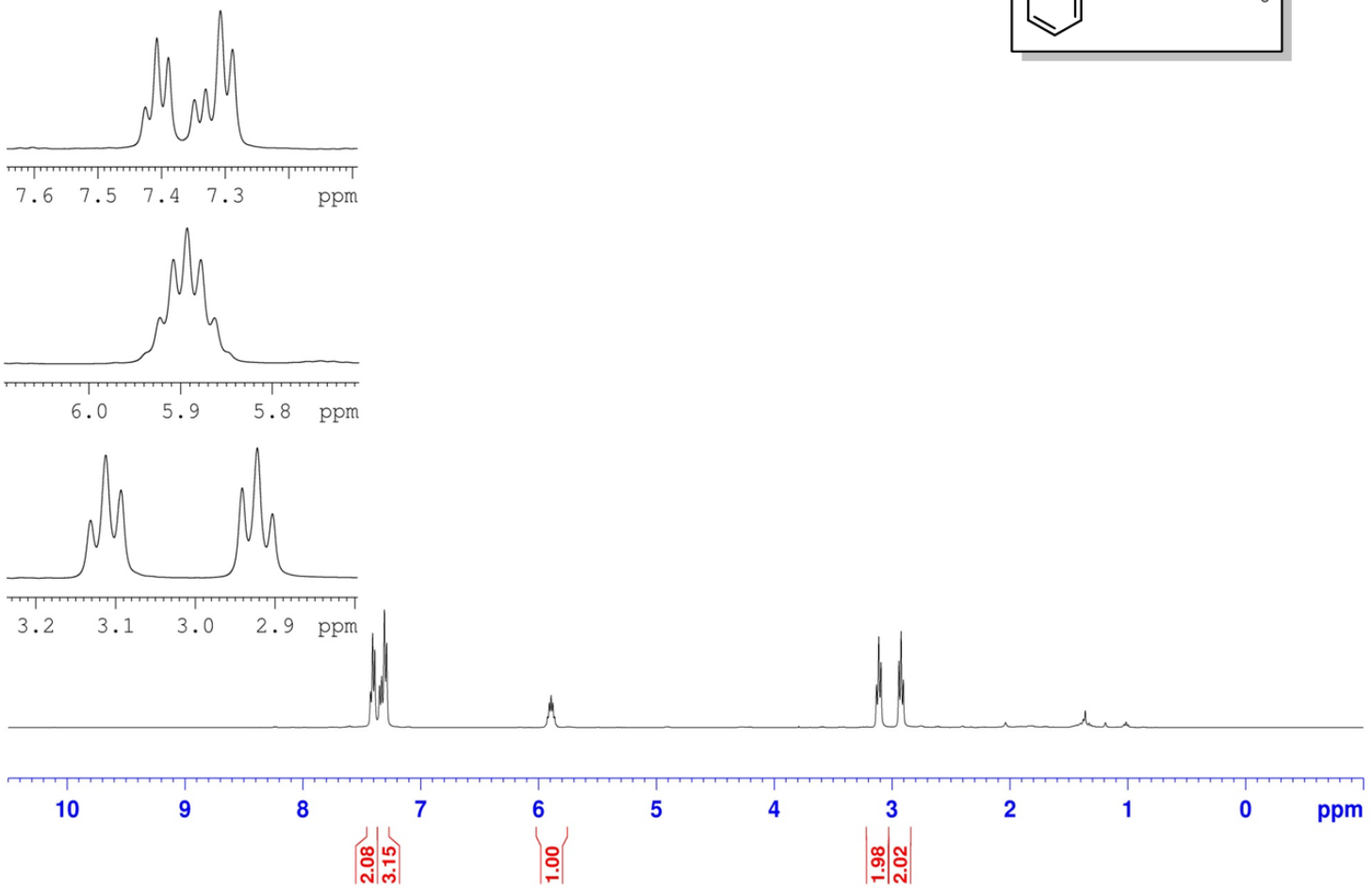
1,1,1,3,3,3–hexafluoropropan–2–yl dodecanoate
400 MHz, CDCl3



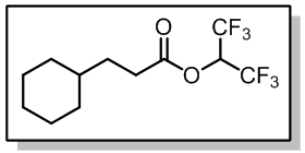


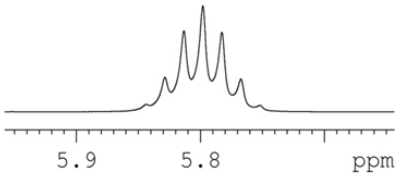
1,1,1,3,3,3–hexafluoropropan–2–yl 3–phenylpropanoate
400 MHz, CDCl3

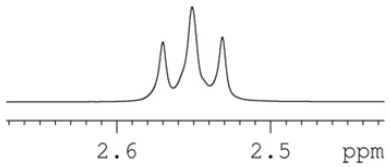


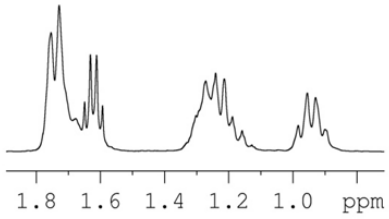


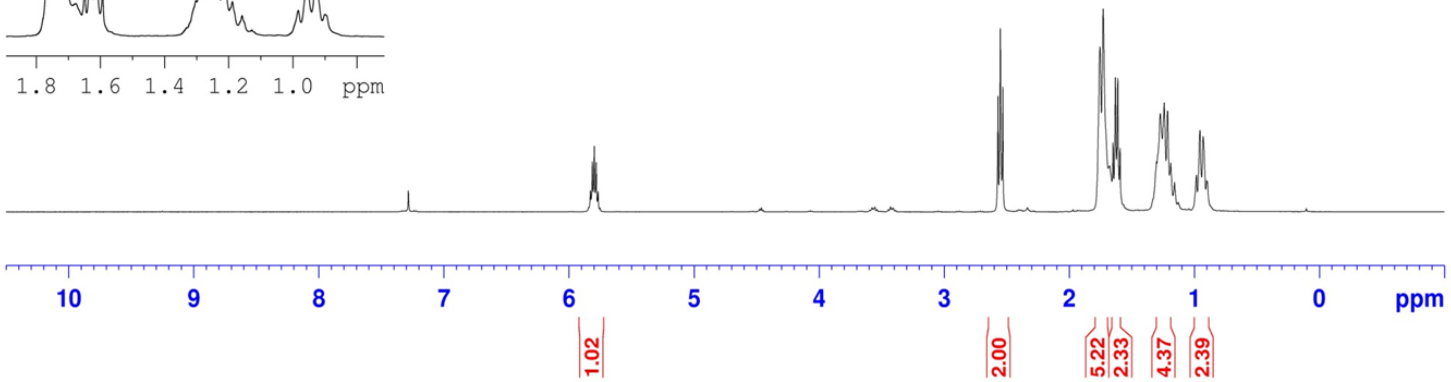
1,1,1,3,3,3−hexafluoropropan−2−yl 3−cyclohexylpropanoate
400 MHz, CDCl3



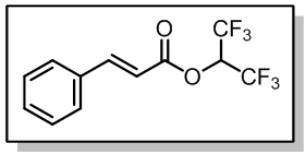


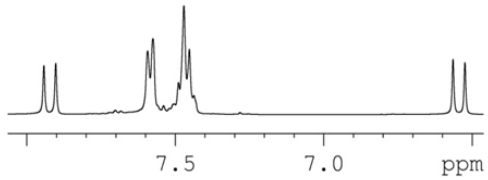


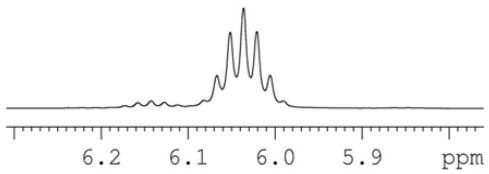


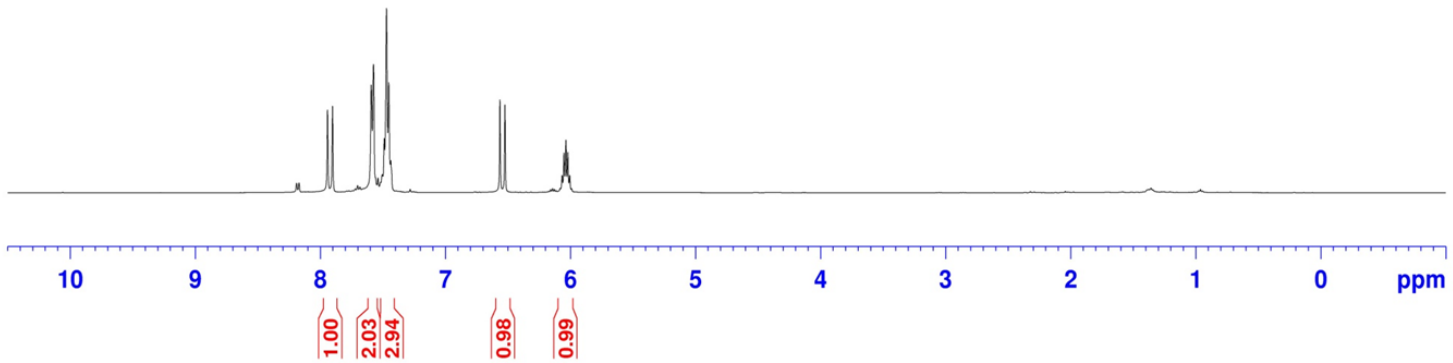


1,1,1,3,3,3–hexafluoropropan–2–yl cinnamate
400 MHz, CDCl3

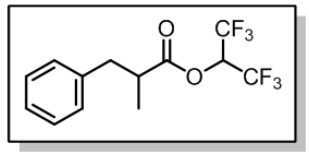


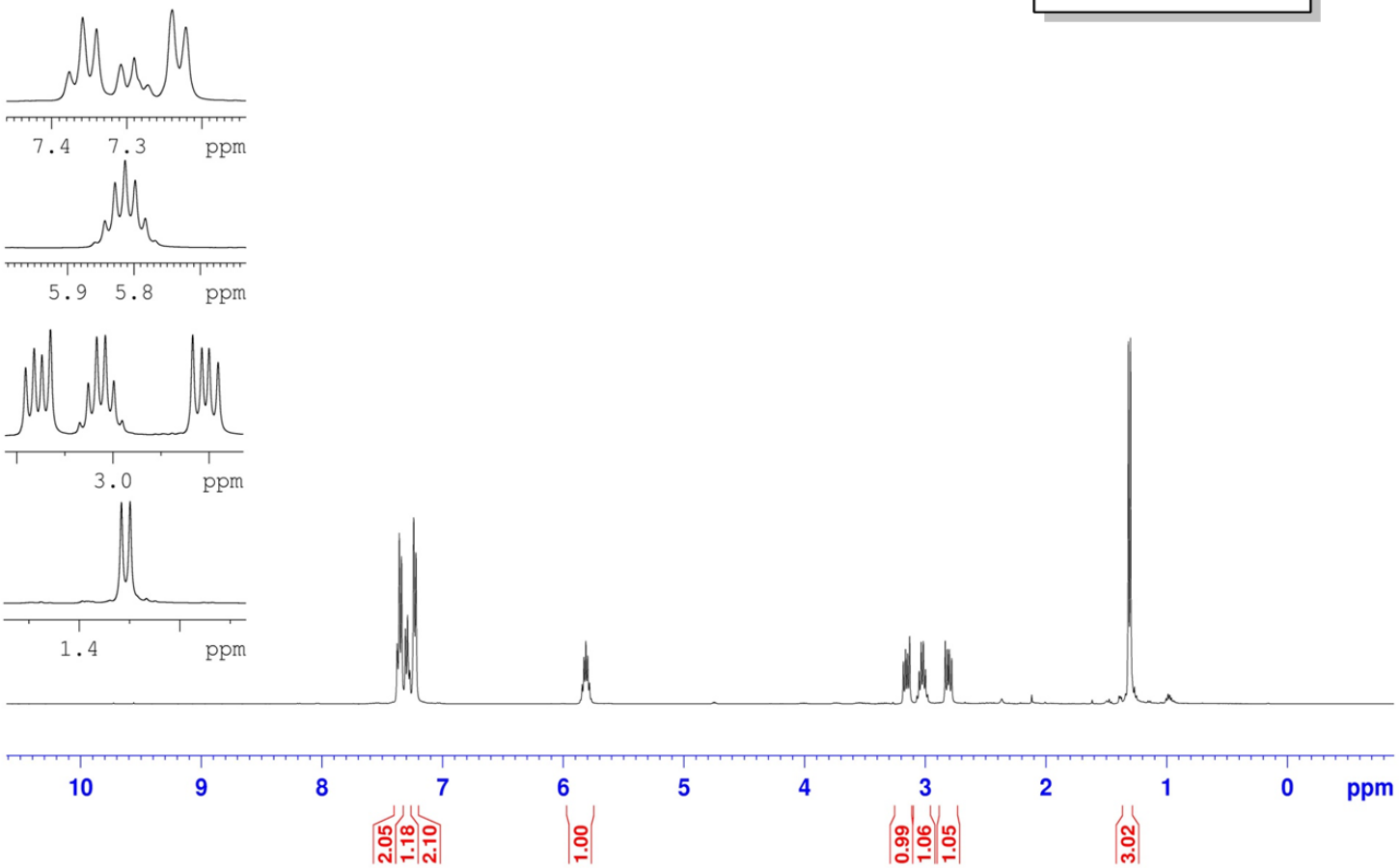




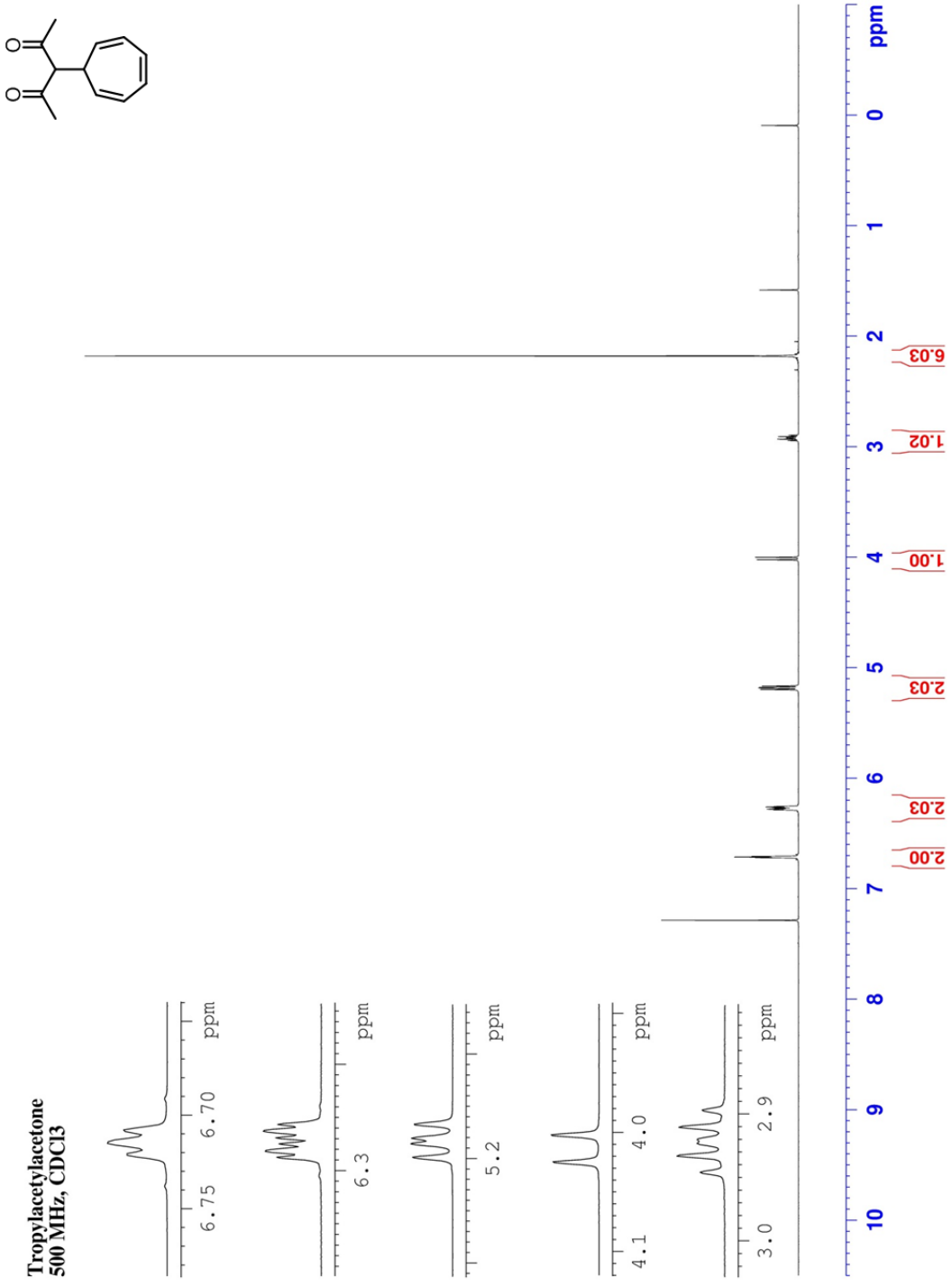


1,1,1,3,3,3–hexafluoropropan–2–yl 2–methyl–3–phenylpropanoate
400 MHz, CDCl3

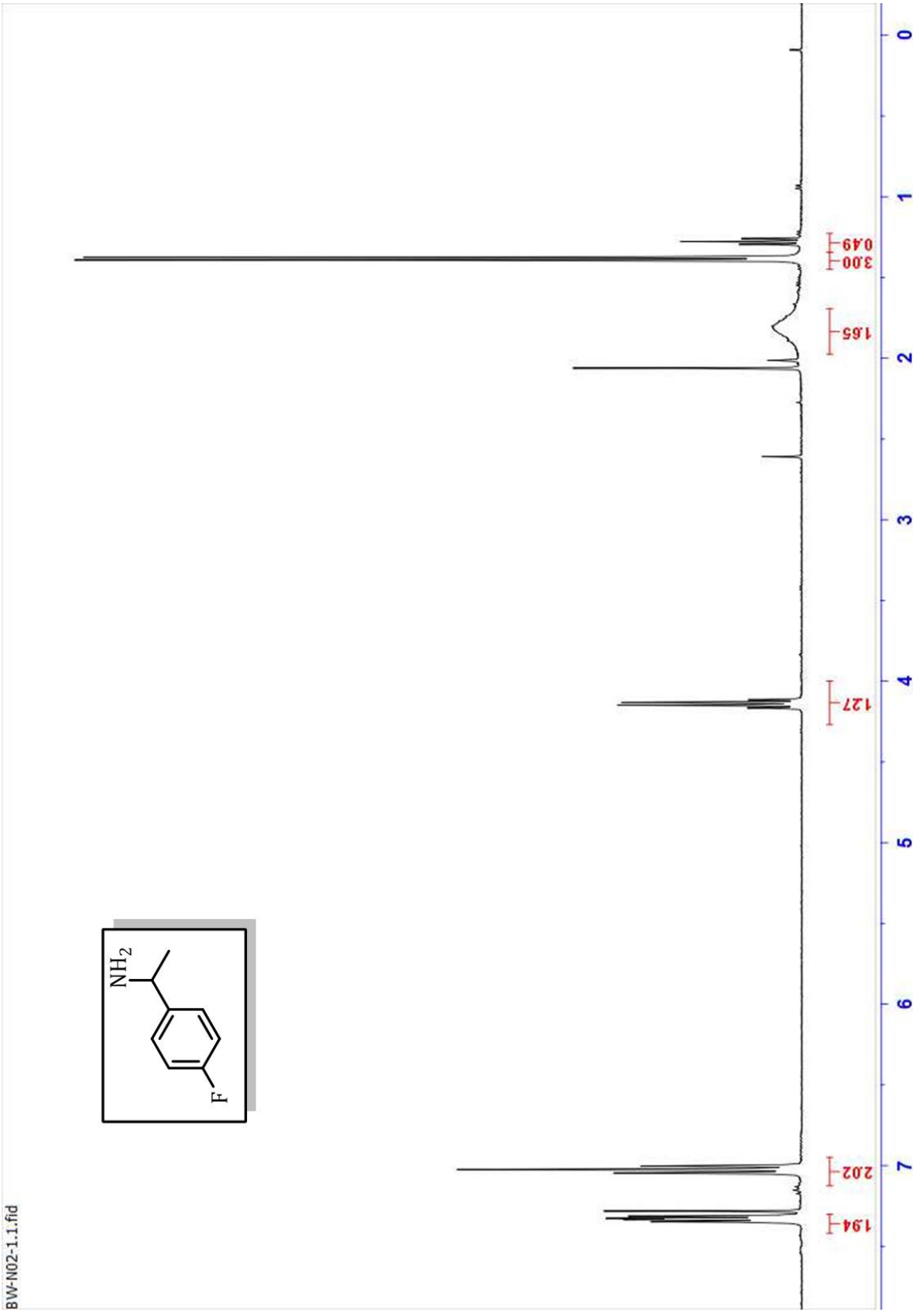


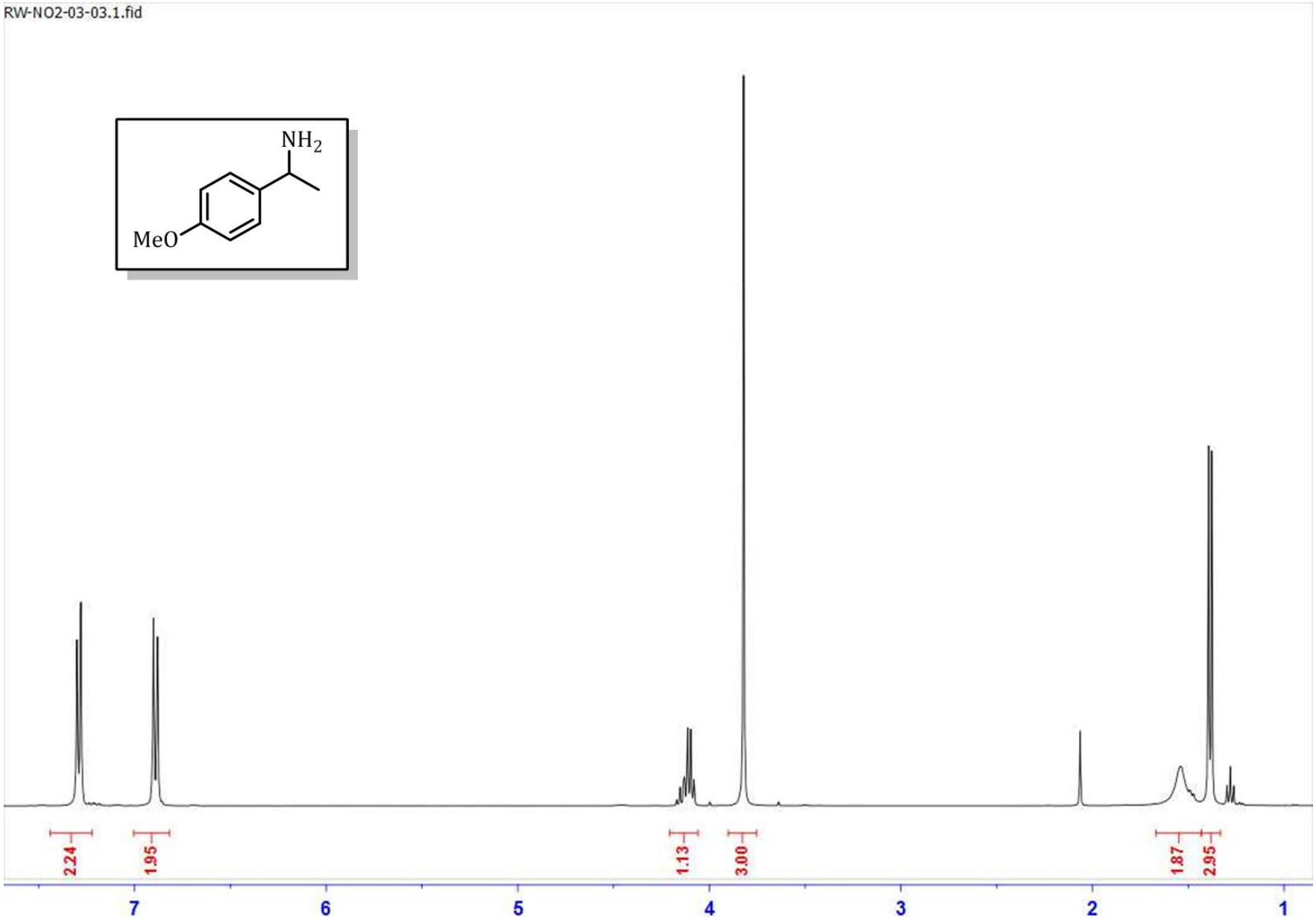


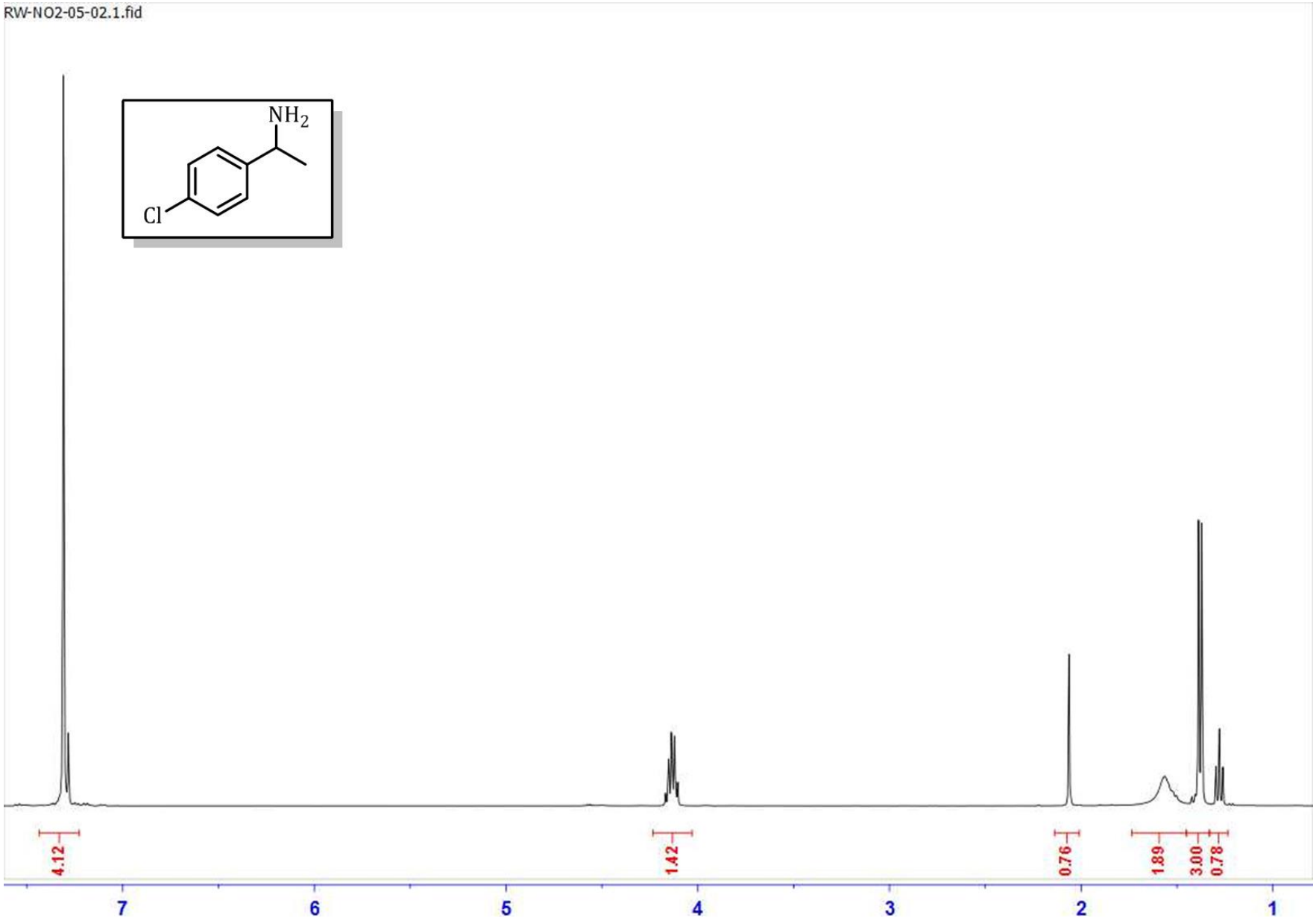
Cycloheptatriene Funcationalization

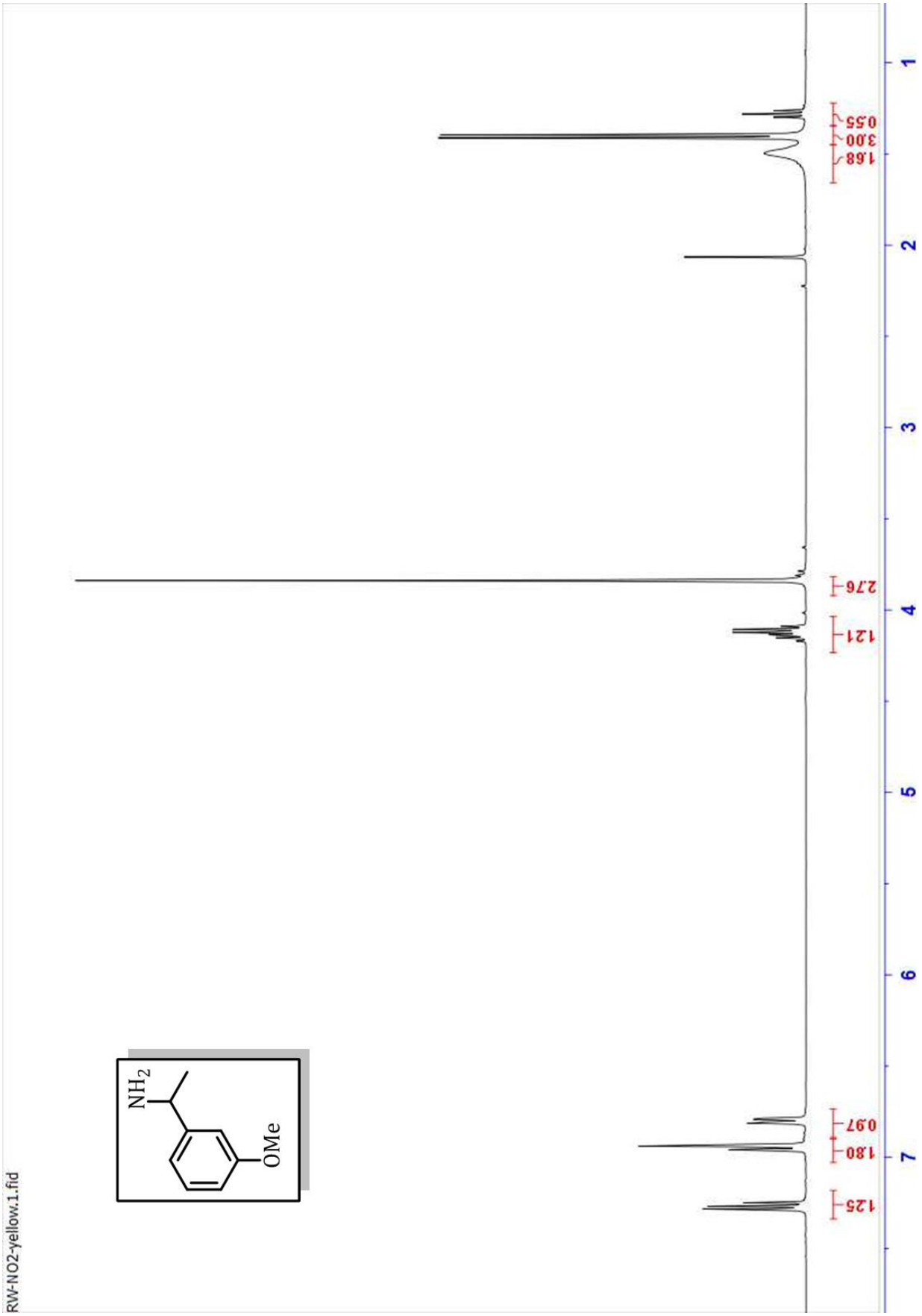


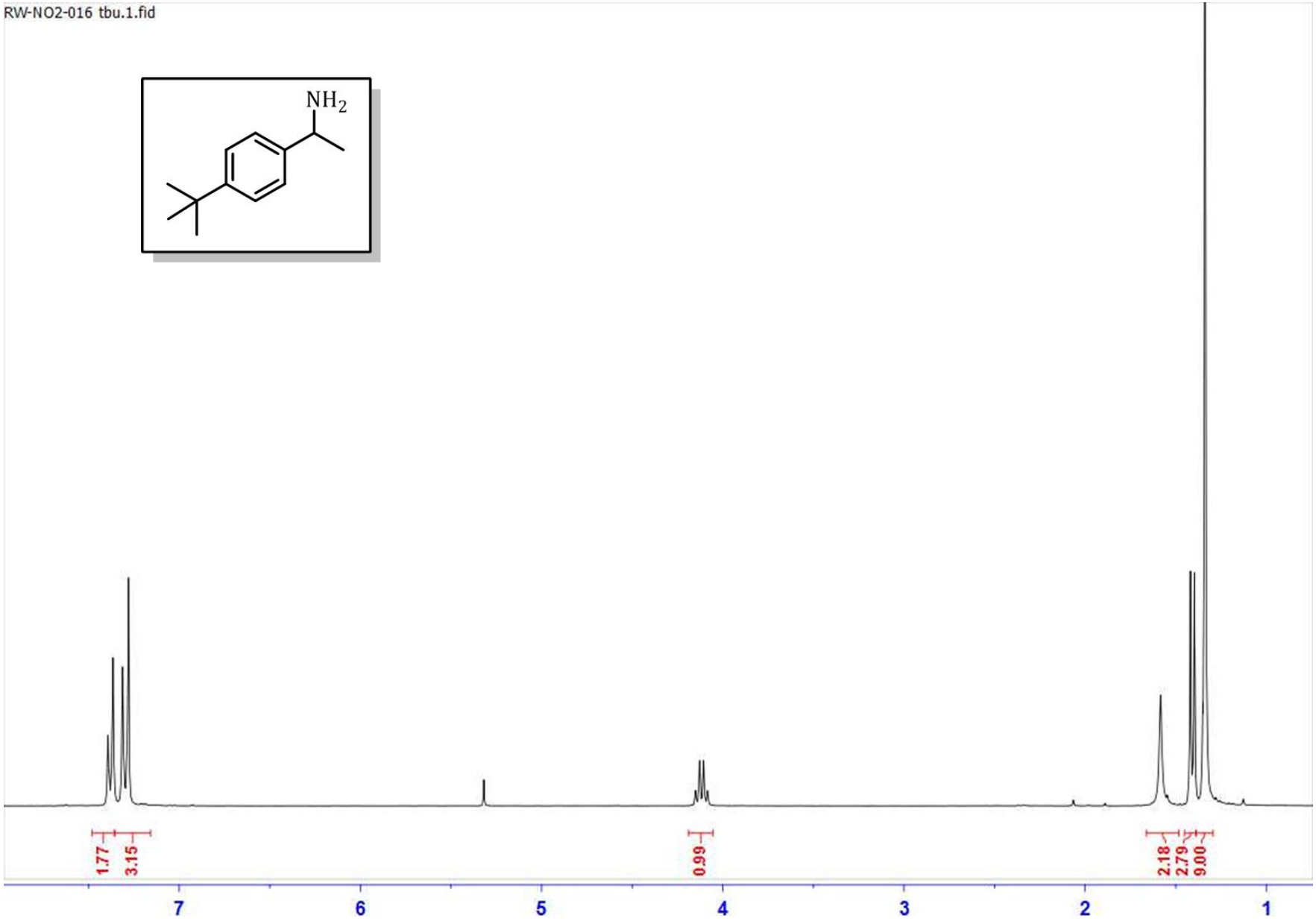
Oxidative Deamination




RW-NO2-03-03.1.fid
NH2
MeO
2.24
1.95
1.13
3.00
1.87
2.95
7
6
5
4
3
2
1


RW-NO2-05-02.1.fid
NH2
Cl
4.12
1.42
0.76
1.89
3.00
0.78
7
6
5
4
3
2
1


RW-NO2-yellow.1.fid
NH2
OMe
125
1.80
0.97
2.76
1.21
1.68
3.00
0.55
7
6
5
4
3
2
1


RW-NO2-016 tbu.1.fid
NH2
1.77
3.15
0.99
2.18
2.79
9.00
7
6
5
4
3
2
1

RW-NO2-017-01.1.fid